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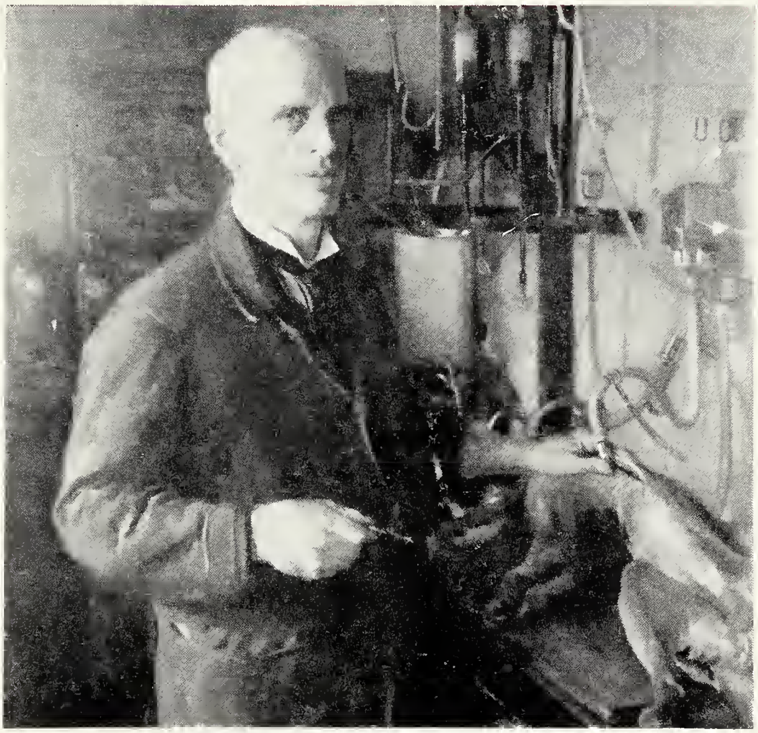

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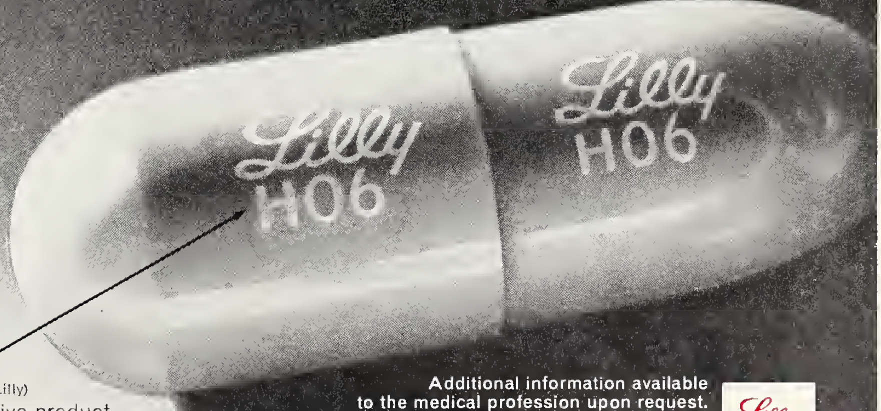

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Connecticut Medicine

editorials

Things To Come

We are in the midst of a revolution in all sciences, especially physics, chemistry, biology and mathematics. What appeared as science fiction a few years ago is coming to be realized today. At least three drugs have been developed that offer advance protection against smallpox, influenza and herpes simplex affliction of the eye. In the case of the first two however the drugs are not effective once the disease has started, but they are helpful in protecting recently exposed persons. This holds up to us the promise of total conquest of disease due to infectious agents, cancer, faulty metabolism and even heredity. It is opening the doors to the last frontiers of the human mind and finally should yield the secret of life itself.

The full potential of the computer will be realized in storage of clinical records, instant recall of information by a physician. Soon the computer will assist the physician in rapid and accurate diagnosis of disease and suggest additional tests to confirm a given diagnosis. This will oblige us to gain a better understanding of the disease process and result in more extensive and accurate description of the disease thereby achieving a proper programming of the computer which will respond to oral and written questions. The physician will be helped to decide what drug to prescribe, their side effects, reactions, dosage, precautions, antidotes, etc.

The computer however will never replace the physician, his reasoning, intelligence and especially the patient-doctor relationship. It will assist him to do his job faster and more accurately providing him with more time for understanding the patient as a sick human being.

Besides the computer many other technological advances will significantly improve diagnostic and surgical technics such as laser beams, neutron guns, simple and more efficient artificial kidneys, heart lung machines, mechanical assists to the circulation. There will be artificial organs such as an implanted artificial heart perhaps made of plastic non-reactive materials, artificial extremities controlled by natural electrical impulses from the patients own nerves so that he can perform intricate tasks. There will be a variety of sensory equipment communicating through the skin so that the blind will "see" and the deaf "hear" with the skin. Artificial substances to replace diseased blood vessels and heart valves are to be improved and special "glues" will all but replace sutures in the surgery of tomorrow.

More complex organs will be replaced by transplantation after the hurdle of the immune barrier

THE COVER

"Science has but one language, that of quantity, and but one argument, that of experiment." These words, spoken by Ernest Henry Starling, describe with remarkable precision the attitude of this great physiologist to science. Ernest Henry Starling was born one hundred years ago, on April 17, 1866. After graduating in medicine he followed his inclination and talent and devoted himself to the study of fundamental problems of medicine, making a number of discoveries in the field of physiology which immediately found medical i.e. clinical application and which have played a significant part in the development of medicine in the present century. With the help of the heart-lung preparation which he developed he succeeded in revealing the basic laws of cardiac activity, in particular the mechanism of adaptation to increased work. His findings and ideas were milestones in the advances made in cardiology and hence in the treatment of heart diseases. His recognition of the fact that the exchange of fluids through the capillary walls depends essentially on the relationship between the capillary blood pressure and the osmotic pressure of the blood proteins was of great significance for practical medicine, providing as it did the basis for our understanding of the pathogenesis of the oedemas and hence also their treatment. It is, of course, not possible to mention all of Starling's discoveries in the short scope of this article; but in conclusion we should like to recall his investigations on gastro-intestinal motility and secretory activity. This work, along with the discovery of secretin, was an essential contribution to the elucidation of the humoral co-ordination mechanisms in the body, and also led to the coining of the word "hormone."—In Starling we honour one of the greatest physiologists of all times.

is overcome and histocompatibility tests will allow for typing donors. Cryogenic technics could allow for storage of organs over long periods. Once the problem of histocompatibility is solved, animal breeds histocompatible with man can be genetically created making an unlimited supply of replacement organs.

Molecular biology, taking advantage of developing knowledge in chemistry, physics and mathematics will elucidate the basic life processes as well as the molecular changes caused by disease. This will require the use of sophisticated equipment such as X-ray diffraction, nuclear magnetic resonance, electronic spin resonance, mass spectroscopy and others yet to come. Knowledge so derived will enable scientists to design and develop tailormade drugs which will treat disease by normalizing metabolic pathways or interfering with abnormal ones, as allopurinal does to interfere with uric acid production. Perhaps this molecular approach may bring about the final conquest of arteriosclerosis, heart disease, metabolic disorders which will loom larger as infections vanish.

Nucleic acid research has already made enormous progress by elucidating the process of heredity and protein synthesis. DNA produces RNA (messenger) which passes out of the nucleus and attaches to two or more ribosomes. Another RNA (transfer) now carries the proper amino acids to the correct position to form protein. The basic code for this process has been elucidated. By changing the code, the cell of one species can be "instructed" to make the protein of another. In this way all life be it plant, animal or human is directed by DNA.

Several transfer RNA's have already been completely characterized and one infectious RNA has recently been synthesized in vitro. In the future what we need to achieve is a nucleic acid free of any disease producing potential, designed in such a way that it will be a kind of artificial virus, free of virulence but retaining its immunizing potential. It will be a kind of chemical microsurgery on the nucleic acid molecule which will then lead to a vaccine to furnish a life-time of protection against one or more virus groups with one vaccination.

Besides prevention, molecular biology should significantly improve treatment. Once the detailed pathways and interaction of the virus and cell is clarified then drugs can be developed which specifically interfere with these processes leading to prevention or arresting a viral infection. We already have Interferon which has a broad spectrum of activity and low toxicity.

From molecular biology we should come to understand how to control cancer and how to fashion broad spectrum antibiotics against most organisms. There will of course arise mutant microorganisms but, armed with deep understanding of all genetic processes, they should offer no serious threat.

Another area in which molecular biology can shed some light, is the question of aging. Is it due to genetic changes in cells as a result of accumulated mutations; is it due to exhaustion of vital enzymes and hormones. We already know that old cells have more chromosome abnormalities than young ones. If we can find ways to stabilize the molecular structure of the genetic material, it may be possible to add many years to the human life span, so that "youth will not be wasted only on the young". Life will then be more productive and more meaningful.

One can predict that the future will have in store for us drugs that will increase the mental capabilities and creativity of normal man. They together with other technics will enhance the learning and thinking process. New chemicals without side effects will serve in the future as tranquilizers and antidepressants. There will be intensive search for ways both psychological and pharmacological so that any one will be protected from developing mental and neurotic illness, but once they develop them to assist the victim to become normal, this includes psychopaths and juvenile delinquents.

Drugs will be made available which will alter human behavior almost at will. Some might make people euphoric and happy, others will put them in a state of sadness. There may appear drugs to influence the soul of man himself, his courage, morals. Man's drive to kill which has been such an ingrained trait derived from his cultural background, may be controlled by proper training and removal of the rewards of war.

The revolutions in physical and biological sciences have had and actually will continue to have a profound influence on all the social behavior of man. It must be compensated for by an increased speed of evolution in social sciences, philosophy and morals. Otherwise tensions will build up and social evolution may be replaced by social revolutions which could conceivably lead to extinction of the human race through atomic nuclear conflict.

We must not forget that technical and physical advancement without a comparable growth in our understanding and mastery of the causes of conflict in society may result in complete destruction of the human race. Let us be watchful that growth of science and technology does not lead to termination of all science, but continue to serve the betterment of the condition of man.

L.H.N.

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Is This Drug Sufficiently Safe For Its Proposed Use?

How extensive are the necessary investigations that must be carried out both in animals and man to answer the question "is this drug sufficiently safe for its proposed use." The question carries many implications. One is that any drug or chemical may present hazards if inappropriately used or even if appropriately used. Many different kinds of chemicals come into contact with man such as drugs, intermediates in chemical synthesis, pesticides, herbicides, household chemicals, fall out products, all of which require safety evaluation.

In the ultimate analysis the safety assessment of a drug relates its usefulness for its intended purpose to its inherent manifestation of toxicity. Any drug can be shown to cause some undesired effects in man when searched for adequately. The undesired effects can vary from minor pharmacodynamic activity to effects which may be hazardous for man and animal. It is for this reason that the determination of safety of new drugs must include consideration of all biological activities as determined in pharmacologic and toxicologic studies in animals and particularly the results of intensive efforts to demonstrate the inherent toxicity of administration of excessive amounts in single and repeated dose experiments.

The major goals in the evaluation of the safety of drugs in animals are: (a) the determination of the type of adverse effects which can be elicited. (b) the exposure levels at which these adverse effects are obtained ("effective doses"). (c) the differences between the effective dose and the therapeutic dose required by the proposed use of the agent (margin of safety).

In man the safety studies consist of pharmacologic and metabolic studies which require one or two doses of the agent and chronic studies wherein the drug is administered repeatedly for weeks or months at doses near the exposure level. In this way it can be determined whether man is not more sensitive (efficacy and toxicity) to the drug than were the animals employed in similar studies.

During the past several years toxicologic and pathologic studies have become extremely important and they incorporate several basic disciplines such as pharmacology, biochemistry, enzymology, nutrition and endocrinology as well as pathology. By this complicated discipline it is possible to determine adverse effects of high doses of a drug on a living animal, the anatomical alterations observed in the tissues of these animals and the selection of doses which will not produce adverse effects. Obviously this means that drug effects must be studied on many biological systems simultaneously in studies which involve continuous administration of large and small doses of the drug for days to many months.

The toxicologist actually practices medicine in reverse. He attempts to produce a drug induced disease in animals rather than to cure a specific disease. This is important in estimating the risk involved in the use of a drug for therapeutic or diagnostic purposes. During the course of toxicologic studies, toxicologists, hematologists, biochemists, endocrinologists, teratologists, pathologists, histologic technicians, doctors of veterinary and human medicine, individuals trained in animal care and the supporting administrative staff including technical writers, librarians, statisticians and secretaries, computers and others are also required. All these individuals play an important role in the conduction of safety studies of new drugs.

When a new drug or chemical is synthesized it is tested in a variety of pharmacologic screening tests with relation to its expected activity according to the class in which it falls. If it shows interesting activity in a certain biologic system (the primary attribute) then intensive studies are conducted to determine its activity in other biologic systems (secondary attributes) which may become potential side effects of the drug. These side effects may actually be the limiting factors in the general therapeutic use of the compound. This type of screening seek effects upon the cardiovascular, respiratory, gastrointestinal, renal, the three parts of the nervous system and endocrine systems. Finally effects on the body metabolism, nutrition, its anti-cancer and anti-infectious properties are studied.

Then must come subacute and chronic toxicity studies in two or more species varying the dose levels above and below the therapeutic level, determining the route of administration and varying it. Laboratory tests of the function of all organs require a high degree of technical skill to detect relatively small damages in dosed as well as control animals. The metabolism of the drug and the effects on the body compounds may be as important for the safety evaluation of that agent as is its effect on the body as a whole. Speed and completeness of absorption, degradation, tissue distribution and elimination must be determined. Effect of the drug on normal metabolic processes, normal body constituents and finally reversibility of the drug effects.

Next comes studies for preclinical evaluation of safety of drugs on reproduction and fetal development which now has come to constitute an important phase of drug safety studies. This involves administration of drugs to animals prior to conception, throughout gestation and effect on organogenesis and dosage relation to fetal death as well as teratologic effects.

Finally pathology studies both gross and histologic must be conducted as an integral part of the prolonged toxicity studies on all organs. Since the changes induced by a drug may be of an entirely different character and may be more subtle than those induced by spontaneous disease it is obvious the pathologist in the drug evaluation team will need special skills and must be supported by an adequate staff of trained histologic techniques including use of electron microscope.

When all the data so obtained are properly assembled it must be submitted to the clinician and governmental agencies. It requires high integrity to rule out errors in the experimental design and cooperation among large members of highly trained individuals with technical ability for the conduction of complicated toxicity studies which may last for many months.

The safety evaluation of a new drug is obviously a fascinating challenge and exacting discipline necessarily requires the cooperative efforts of scientists of high competence and integrity drawn from many disciplines. Clearly the pharmaceutical laboratories which are drug oriented and have the goal of producing useful, safe new drugs are the place where cooperation and coordination of many different scientific disciplines are united in the same research organization. They are excellently equipped to carry out drug research and the patient and physician are their beneficiaries.

If one is asked the question why drugs cost what they do, the skills and technics of evaluating drug usefulness and safety mentioned above provide the rational explanation.

L.H.N.

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Oxygen Sensitive Arteries

We are accustomed to think of physiologic expansion and contraction of arteries as a response to the action of neurohumors upon the smooth muscle cells in the arterial wall. That this is an oversimplified concept can be seen in the cerebral arteries where sympathetic control is minimal and where the arteries open when pCO_2 rises or pO_2 falls, and conversely constrict when pCO_2 falls and pO_2 rises. The sensitivity of cerebral arteries is very high in neonatal retinal vessels which have been seen to constrict to obliteration if stimulated by high enough pO_2 producing retrolental fibroplasia[2].

If the cerebral vessels are particularly sensitive to pO_2 in the neonate, can oxygen be the physiological stimulus for contraction and closure of the ductus arteriosus and even for contraction of the aorta in the region of the ductus termed aortic coarctation. We know that in most instances the ductus closes with onset of respiration[3]. Kennedy and Clark's observation on guinea pigs showed that it was initiation of breathing that caused ductus constriction but only if O_2 was present in the inspired air. Many others have shown in the intact animal that administration of O_2 rich gas closes the ductus and that breathing anoxic gas can reopen the ductus in the first few days of life.[4] Finally Assoli et al[5] and Kovalcik[6] each showed that contraction can be produced in the isolated ductus when the O_2 tension is raised.

The degree of ductus contraction then is a function both of the O_2 stimulus and of the amount of oxygen sensitive muscle cells present in the ductus. Looked at in this way absence of the oxygen stimulus should keep the ductus open in the neonate, but also a congenital inadequacy of contractile elements. If the oxygen stimulus is poor there should be more patent ductuses and this in fact was shown by Pènaloza who found in a survey of those living above 10,000 feet altitude an incidence of patent ductus arteriosus of approximately one per cent of the population living at high altitudes an incidence many times that found at sea level. Why any one should have a patent ductus at sea level where the oxygen stimulus is adequate remains to be explained. Perhaps pulmonary ventilation is inadequate in the first few days of life or perhaps an inadequate amount of smooth muscle is present in these ducts.

The question now arises if C_2 causes constriction of the ductus arteriosus what does it do to the reactivity of the neonatal aorta. This question is important both theoretically and practically. If enough O_2 sensitive tissue exists in the preductal region as it does in the ductus, then it should produce a constriction at that point when the O_2 tension is increased. If too much O_2 sensitive muscle is present can this be the reason for the occurrence of aortic coarctation which almost always occurs in the preductal region. Furthermore what would happen in the neonate who is given O_2 in high concentration for any reason?

Gilman and Burton[8] by a special perfusion method were able to measure aortic and ductal responses to increasing and decreasing pO_2 in the perfusion fluid. They confirmed previous observa-

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tions that as soon as O_2 was administered instead of N_2 the ductus closed within three minutes. In the aorta, constriction was also observed except the phenomenon was slower in developing. As the retinal vessels, the aorta also was extremely sensitive to O_2 at birth, maximal at one to two days after birth and very small after seven to eight days. It was clear also that the part of the aorta most sensitive to O_2 was the preductal area, just the place where infantile coarctation is most often found.[9,10]

The response varied from animal to animal. Puppies aortas were hardly sensitive, while that of rabbits reacted to a lesser degree than the aorta of guinea pigs. Doubtless this probably means variation in the amount of contractile tissue present, although one cannot rule out variability also in sensitivity of the contractile tissue to O_2.

Despite marked species differences, one thing common to all is that the aorta in each species behaves in a manner similar to the ductus. However the sensitivity of the aorta to O_2 appears to be much below that of the ductus and it appears to retain its sensitivity to O_2 a little longer. The interesting physiological parallel between ductus and aorta warrants our being cautious in administration of O_2 rich gases to the normal neonate. It may have no serious consequences in the aorta (that is aortic constriction may be slight and temporary). However in the case of a congenital anomaly in the location of O_2 sensitive tissue between the ductus and aorta, an anomaly consisting of increased amount of muscle cells than O_2 administration might precipitate permanent aortic coarctation.

To the known hazards such as atelectasis and retro-lental fibroplasia, we must now add another hazard to O_2 administration to the newborn, namely aortic coarctation.

L.H.N.

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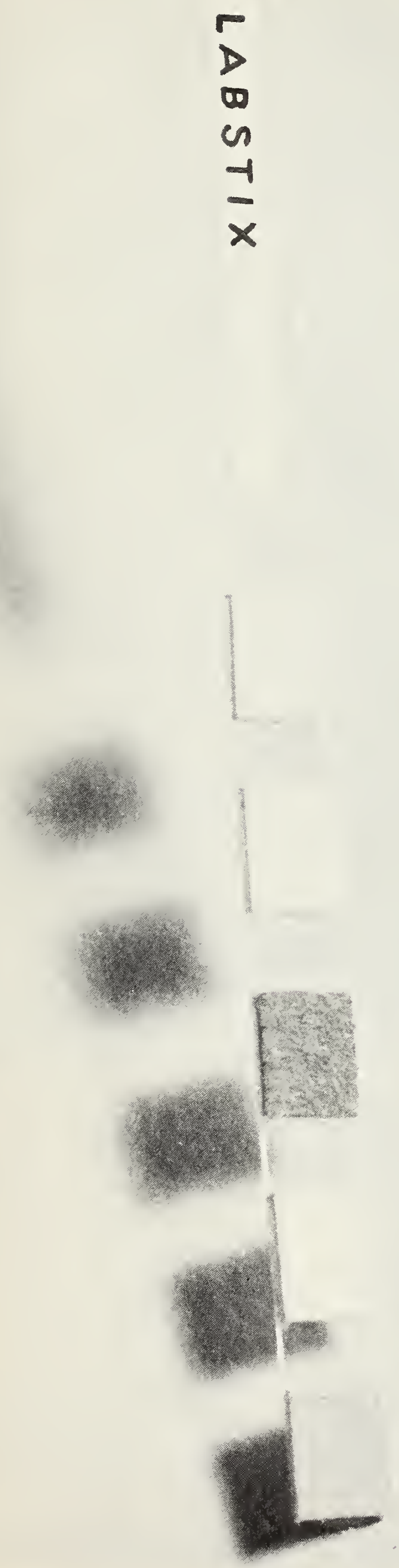
Science Tools: Tissue Culture

Tissue culture has now become a major tool in biology. It originated in 1906[1] when the Nobel Laureate Ross G. Harrison succeeded in growing nerve fibers outside the body. It lay practically dormant until the middle of this century when Enders et al[2] cultured poliomyelitis virus in human embryo cells. They laid down the fundamental principles and procedures for tissue culture propagation of viruses.

In 1950 Eli Lilly & Company[3] established a laboratory specifically devoted to the study of tissue culture and this was shortly followed by many other laboratories. Now there are numerous types of tissue culture which the biologist employs for his needs; primary cultures prepared directly from tissues of animal hosts, continuous cell cultures which can be serially passaged in vitro, and an intermediate type introduced in recent years by Hayflick and Moorhead[4], known as "diploid cell" line which can be serially propaged but have a limited life span.

The most popular primary culture system is a monolayer culture of tissue cells first treated with trypsin to remove the intercellular cement, and then inoculated into a suitable culture vessel.[5] Here they form a monolayer of cells growing on a glass floor of the vessel. Another primary culture system consists of fragments of tissue embedded in a clot of chicken plasma. The cells grow out of the fragment in a radial pattern and are highly useful for growth of poliovirus. It is the new growth of cells which is largely responsible for the yield of virus harvested from these cells.

The continuous cell strain is the most widely employed of any type of tissue culture. There are hundreds available from a great variety of animals from amphibians to man. The majority are connective tissue or epithelium and many are from human tissue. Pure cell strains have been developed by this technic and grown in tube culture, bottles,



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flasks or Petri dishes. Fluid suspension of cultures for large scale production of cells lends itself to quantitative technics.

The diploid cell line is one in which the majority retain the normal diploid number of chromosomes present in cells of the host species. Human cells so grown are especially useful in growing viruses infecting man and also of value in vitro studies of carcinogenesis.

There are a variety of technics for developing and identifying cell strains. They can be experimented with appropriate technics for freezing, cold storage such as preservation for sperm banks. Many other problems relating to tissue culture include a study of growth factors and inhibitors, chromosomal analysis, malignancy, testing of cell strains for the effect of drugs. Culture cells or the spent medium from cultures are being examined for pharmacologically active substances.

The use of tissue culture in virus research is indispensable. Many viruses hitherto not isolated can be separated and grown by this technic such as cold viruses, hepatitis virus, Simian virus 40 from kidney cells formerly used to produce and test virus vaccines. The mechanism of virus infection and multiplication in tissue cells has been elucidated and the role that nucleic acid and certain cellular enzymes play in this process. With radio active materials one can investigate how a viral protein directs the synthesis of viral protein and the complete viral particle. The electron microscope has helped to tell us about the size and configuration of viruses and changes occurring in various stages of infection of a cell by a virus. Also studied by the virologist in cell cultures are anti-viral chemo therapeutic and chemo prophylactic agents, diagnostic antigens or vaccines for immunization and interaction among cells, drugs and viruses.

Virus replication is a prime model for study of the transfer of the genetic code and the resulting syntheses of protein and nucleic acid. Virus replication in a cell is an excellent model to study each segment of the life cycle of viruses and how they multiply. Once we know the life cycle of a virus we are free to find a drug which can inhibit each step, one that can block penetration of the cell by the virus or one that can prevent multiplication once the virus has penetrated the cell. Without doubt as tissue culture technics for detection of viruses improves the chance for a breakthrough in virus chemotherapy becomes greater and greater.

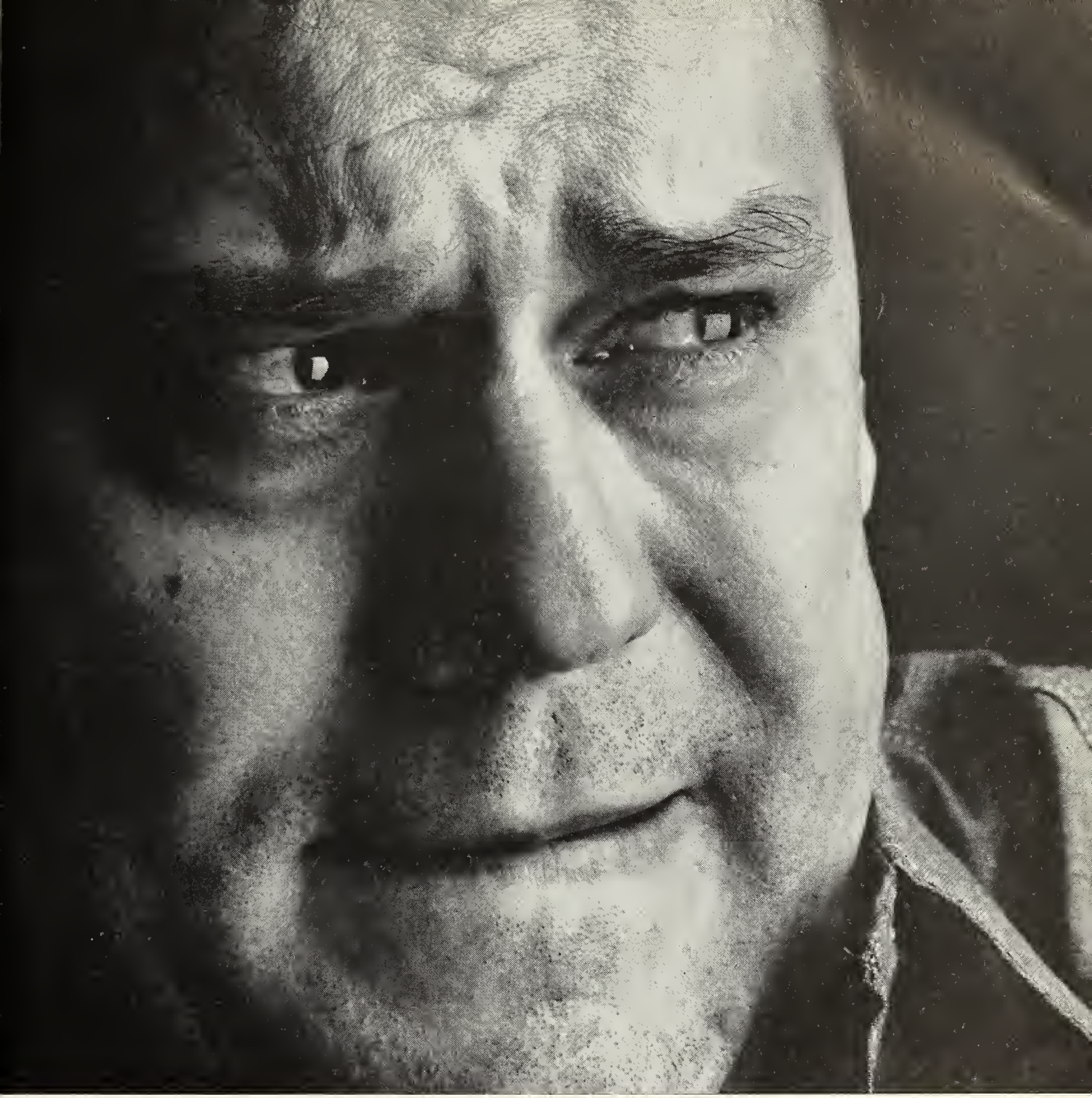
A wide range of host cells can be studied and the best methods of virus assay and production will become available. What is the optimum levels of the inoculum, the temperature of incubation, proper medium constituents, time of harvest to assure maximum viral yields. Technics for inactivation without loss of antigenic potency, a search for attenuated strains and even fractionation of viral particle to evaluate subviral components as immunizing antigens are but a few of the problems readily solved by the tissue culture technic.

Tissue culture has proved to be an important tool also in cancer research. One can study tumor viruses as well as the intimate relationship between two oncogenic viruses in cell culture. One can use it as an adjunct to histopathologic diagnosis of malignancy, for studies in carcinogenesis and assessing malignant potential of cultured cells. One can study metabolic differences between normal and malignant cells. One can search for anti-tumor agents by screening large numbers of chemical compounds and fermentation products. How do such agents act? What cell functions are involved? How to design a more effective compound from a diseased anti-tumor agent? Those answers will be forthcoming from the highly trained teams of biologists, physicists and virologists now working in a great number of laboratories of our pharmaceutical industries.

It is in those laboratories Hull, DeLong and Johnson point out that many of the successful technics for tissue culture have been developed. Now they have cultures of kidney tissue for polio vaccines in 1200 liter flasks. For the production of measles virus vaccine monolayer cultures of chick embryo cells are employed. Now Hayflick[6] points out that human cells from a healthy embryo lung the size of a finger tip could be used to produce twenty million tons of cells. There is no danger, that extraneous virus might be present in such cells and standardization is much enhanced because they are derived from the same material and this latter factor makes for inexpensive production.

This technic can revolutionize the production of vaccines. Already vaccines against adenovirus 4 has been fed to 50,000 military recruits with no untoward effects and a marked reduction in infection from this virus. Another vaccine, polio vaccine, produced in cultures from the same human cells has been used by more than 250,000 children in Yugoslavia without any untoward effects. It is interesting that the original human cell source for both of these vaccines was just one finger tip size piece of healthy human embryo lung obtained in Sweden five years ago. Human embryo cells from one piece of tissue thus has come to be receptive to growth of many viruses that naturally affect man and which is not always true of animal cells.

It has been pointed out repeatedly that one new technic can accelerate the development of knowledge many fold. This was true in the recognition and purification of Thymosin[7] and now is true in the study of the rapid acceleration of knowledge of



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viruses, cancer, the genetic code by the development of tissue culture as a tool of research in these and many other areas.

L.H.N.

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Safety Of Our Food Supply: Physiologically Significant Food Contaminants II The Mucotoxins

Some types of plants concentrate toxic substances from the soil. It is known that selenium is a dietary essential for cattle and sheep and a condition known as "white muscle disease" develops in areas where the soil and therefore the forage is deficient. The opposite is also true, namely that frank hazard to the livestock occurs in certain localities where the selenium content is too high. The hazard arises because some weeds are able to accumulate selenium in toxic amounts and when ingested by foraging animals give rise to selenium poisoning known as "alkali disease". Seleniferous weeds convert selenium to a form which can be used by forage plants and even cereal crops which when grown in such areas contain toxic amounts of selenium.

Another contamination of forage plants is by the genus Seneca which contains quantities of a pyrrolizidine alkaloid capable of causing liver damage. Apparently this is a problem in domestic animals all over the world eating wheat contaminated by these weeds but it also causes "bread poisoning" in man. A similar problem is found to occur where "bush teas" are made from wild plants including Seneca and frequently used as folk medicines. Veno-occulisve disease from such teas has led to many deaths, especially among young children in Jamaica.

Food contamination by secondary mold metabolities represents an important problem only fully realized in the last decade. The growth of contaminating fungi are liable to affect the majority of food crops at some stage during their harvest, storage, transport, or processing. Mold spores are distributed on practically all crops and subsequent sporulation and mycelial growth are then determined by conditions of moisture and temperature of the crop during the period from harvest to final utilization.

During the entire post-harvest period the crops are essentially in a stage of storage and subject to damage attributable to attack by fungi, insects, and rodent pests. Commodities particularly prone to this sort of damage include fruits, vegetables, grains, and oilseeds. One estimate places the total annual world-wide grain loss alone from all causes at 55 million metric tons, much of it due to molds. The post-harvest loss of fruits and vegetables in the United States alone is equivalent to one out of every eight acres producing these commodities. These mold growths produce many deleterious changes in various crops such as discoloration of cocoa butter, rice, loss of seed viability, mustiness of coffee beans and lipolysis of fats and oils.

These deleterious effects of molds result in significant economic losses by decreasing the world food supply. However in some instances fungal spoilage contaminates the commodity with toxic metabolites produced during mold growth and called mucotoxins. One long recognized is ergotism which arises from the growth of the mold Claviceps purpurea on rye and other grains.

Another mucotoxicosis was found in Russia during the war years when millet was not harvested because of manpower shortages, stayed in the fields over winter and spoiled by mold. It caused leucopenia, agranulocytosis and death from secondary infection.

In Japan rice is stored and transported under conditions that may lead to growth of fungal contaminants. These fungi produce toxic metabolites causing a beri-beri like type of neurologic disease.

There are numbers of obscure diseases in cattle caused by mucotoxicosis. One is caused by a mold growing on rye grass pastures. Another caused by an aspergillus species causing moldy corn poisoning. Then there is the aflatoxin problem which has come to light since 1960. Large losses of turkey poults, and ducklings in England and Kenya was found to be due to a Brazilian peanut meal which was spoiled by an aspergillus flavus. There was extensive liver damage in these birds and the toxin was hepatocarcinogenic both in the rat and hatchery reared rainbow trout. Mucotoxin contamination thus can enter human foods either by direct entry at some stage of production or by indirect

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*Brest, A. N., et al.:J. New Drugs 5:329, 1965.

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contamination by accumulation of residues and metabolites in animal products used as a food.

What has been said above indicates clearly that mold contaminants of food are not always the inocuous nuisances they have sometimes appeared to be. For a number of them are obviously capable of contaminating the food chain with potent compounds. But the food chain is not the only way in which mold contaminants can affect human health. Recently Forgacs and Carll isolated a toxic substance from tobacco caused by a species of Alternaria and Aspergillus niger which was very toxic when taken by mouth and when the contaminated tobacco was smoked it led to emphysema and in some instances alveolar cell carcinoma in mice. These workers found a very high percentage of heavy contamination in cigarette tobacco.

There will need to be accurate evaluation of the mucotoxicosis problem. The question of mocotoxicosis is particularly pertinent in those geographic areas where relatively restricted populations regularly use diet components that are exposed to significant mold contamination. They may have food habits depending on use of fermented products using natural inocula under uncontrolled conditions Fortunately, however, a relatively small proportion of field and storage fungi are toxin producers. Mycotoxins are probably produced mainly during the immediate post-harvest and early storage periods when the moisture content of many commodities is sufficiently high to permit sporulation and growth of contaminating molds. The general problem would therefore appear to be amenable to control by the application of such measures as rapid drying, improved storage and transportation conditions as well as possible use of fungicidal agents.

Perhaps if tobacco were treated this way it might be possible to eliminate at least one factor producing lung disease in cigarette smokers.[3]

L.H.N.

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The Microcirculation: III. Regional Impairment And Its Management

The success or failure of a carotid endartectomy will depend first of all on the restoration of adequate blood flow through the stenosed arterial segment. But it will also depend on the state of the terminal vascular bed. Atheromatous embolization as well as the duration of carotid artery thrombosis are of course recognized factors. What is rarely thought of is the possibility of failure of the cerebral autoregulation when the sudden inflow occurs in the ischemic area immediately following restoration of the circulation. We could be helped in this regard if accurate and clinically feasible tests for the adequacy of the cerebral microcirculation were available. Unfortunately they are not.

When it comes to the renal microcirculation, we have a strictly analogous problem, to that of the cerebral circulation, for here also it is necessary to differentiate between the cause of the circulatory impairment, namely whether we are dealing with extra-renal or intra-renal vascular disease or both. It is customary to resort to a battery of tests such as a timed pyelogram, retrograde aortico-renal angiography and bilateral percutaneous renal biopsy. If the renal arterial stenosis identified by the angiogram is simply removed without any knowledge of the state of the renal microcirculation, one may not be able to foretell the hypotensive effect on the procedure.

Even if the contralateral kidney is not ischemic, a cure for the hypertension does not necessarily follow after correction of the renal arterial stenosis, because the opposite side may have intrarenal disease. In some patients in fact the severely involved terminal vascular bed will have lost its autoregulation and will decompensate when confronted with a new pulsatile mass of blood.

The splanchnic pool contains a great volume of blood which controls right atrial pressure. It is also the site of massive vaso-constriction in shock which can be relieved by coeliac plexus block. We already know that severe vaso-constriction can lead to hepatic, splanchnic or intestinal necrosis. There are also milder forms that can be detected by electron microscopy of biopsied material.

Mesenteric thrombosis is encountered in patients in whom the major arterial and venous pathways are intact. Release of ischemia produced by clamping the aorta and then releasing the obstruction may produce hypotension and metabolic acidosis. In man acute hypotension may develop in as much as 20 per cent of patients after resection of an aortic coarctation.

The sudden encounter of a lack of autoregulation in a previously ischemic area is of fundamental physiological and clinical importance. In the lower extremity, it may take from 1-9 weeks for the peripheral resistance and blood flow to become normal. Urgent fasciotomy to prevent muscle necrosis is sometimes necessary following reconstructive arterial surgery. In the tight muscle compartments of the leg, the sudden hyperemia and capillary leakage immediately after the reconstructive surgery could otherwise seriously prejudice the vitality of the muscles.

Deep venous thrombosis is also associated with microangiopathy. For example in phlegmasia cerulea dolens, the venocapillary bed is also filled with thrombi. Only early and extensive femoral thrombectomy with evacuation of both the proximal and distal segments can clear the microcirculation. De Takats[1] points out that sympathetic block is ineffective and so is regional heparinization. He thinks that Dextran 40 applied through a drip into the affected venous segment may help and certainly is worthy of trial.

In the therapy of the acute microangiopathies, basically one requires adequate perfusion. Of the desludging agents Dextran 40 heads the list. Of the antithrombotic agents, heparin and plasmin head the list, but obviously one must be sure they are used only in diffuse microthrombosis and this can only be established by laboratory studies.

Vasoconstrictors are seldom used unless there is present a state of low peripheral resistance. This can readily be established by a sensitive digital plethysomograph which gives quantitative information regarding peripheral resistence in the vessels of the extremities.

Of the vasodilators isuprel seems effective since it also increases myocardial contractility. Some have also advocated chlorpromazine.

One of the basic defects namely hypoxia of the tissues in microthrombosis are associated with metabolic acidosis. To reverse the acidosis $NaHCO_3$ and other antacids are valuable. To combat the microthrombosis determined from a study of the clotting time one must logically employ thrombolytic agents and especially heparin. de Takats has used sodium thiosulphate, a chelating agent to reduce the acute inflammatory phase of microvasculitis. It also acts on the clotting mechanism and may well influence the local antigenic response.

In chronic microangiopathies, the lesions are much less reversible. Anti-inflammatory agents, steroids, chelating agents and immunosuppressive drugs all have their proponents. It is however difficult to see how a chronic necrotizing ateriolitis would respond to any form of therapy except in the acute stages when antiinflammatory drugs and/or steroids may serve to bring on a remission.

We can see that the microcirculation, the "third force" is where the business of life is accomplished. However as the capillary flow decreases or damage to the endothelial surface occurs, then a shift in the pH to the acid side, and widely disseminated intravascular microthrombosis takes place and this in turn uses up the available fibrinogen. This in turn results in the depletion of hemostatic components. Sudden restoration of blood flow in a chronically compromised area destroys its autoregulatory mechanism and could prevent the benefits from a restored circulation.

To restore perfusion pressure, to combat acidosis, to treat the microthrombosis, to avoid endothelial damage in autoimmune disease are the objectives to be sought when dealing with disorders of the microcirculation.

L.H.N.

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Transplantation Biology: III. Improving Clinical Results

Since 1955 more than 1,000 people have received kidney grafts, but because its results are unpredictable, the procedure must be considered purely experimental. To be sure, immunosuppressive drugs can frequently keep a host's resistance to a homograft in abeyance for up to a year or more in exceptional cases. Obviously success depends on the ability to find a dosage of the drug that will suppress the homograft reaction without, at the same time, impairing the host's immunological machinery to an extent that renders him incapable of coping with the common pathogens of everyday life.

The results of course are very much better when donor and host are related as between parent and offspring or between full siblings than when they are unrelated. This raises the question as to whether there are histocompatibility group systems among man as there are compatible blood types. How many histocompatible types there are and how to recognize them? Perhaps this knowledge would then permit us to match or type donors and recipients and enable surgeons to exclude donors whose grafts would be grossly incompatible for a given recipient.

Effective means of selecting the most compatible donor from a small available panel now seems almost within our grasp. Obviously the ultimate goal is to develop highly specific monovalent antibodies capable of identifying at least the more important transplantation antigens that contribute to a person's antigenic uniqueness. Then individuals will be typed with respect to their transplantation antigens as they are presently typed with respect to their blood groups. In the process we will learn a lot about the genetics of tissue incompatibility in man concerning which we know practically nothing at present. Once this is achieved, transplantation of tissues and organs will have emerged from the experimental into the clinical realm.

At present we are forced to rely on immunosupressive therapy by a variety of means to prevent the host's immunological attack against the graft, an attack usually of sufficient intensity to impair its function and threaten its life. The attack must be detected early enough so that this reaction can be reversed. It is accomplished by treating the patient with corticosteroids, actinomycin C and other agents such as x-rays.

Once the immunological attack has been turned, it may remain quiescent for a long time. Clearly an understanding of the processes underlying such delayed attacks could be of utmost importance, for it may indicate the total destruction of a specific immunological active lymphoid cell population. Or some other obscure mechanism is operative which we could harness in future transplants if we understood its nature.

Billingham points out that there are different types of investigation that should lead to considerable improvement in the outcome of clinical homotransplantation in addition to histocompatibility typing. One is development of more effective and more selective immunosuppressive drugs. But to accomplish this we must realize that both lymphocytes and humoral antibodies are involved in graft destruction and each requires a different approach. Many authorities believe that the proximate "cause of death" for a homograft is the cytocidal properties of immunological active lymphocytes. How is this cytocidal effect mediated? Is a cell-bound antibody involved or is it due to some kind of pharmacologically active substance analogous to histamine. If the latter then we could proceed to discover a pharmacologic antagonist.

The ideal solution of course would require a treatment that could render the host completely and specifically tolerant of the alien antigen of his homograft. This would obviate the requirement for continued drug therapy with all its undesirable side effects. The principle of immunological tolerance applies to adults as well as infants. However to induce this state repeated doses of homolagous cellular inocula are needed to overcome the major incompatibilities and these amounts may be too great. In mice they may amount to several donor equivalents of splenic cells. This approach in man would fail because of insufficient available donor cells and the risk of causing harmful graft versus host reactions on the part of the inoculated ingredients of the host donors lymphoid system against the foreign antigens of the host.

However it may be that partially degraded antigens can lead to tolerance and they may do this more effectively if administered in conjunction with immunosupressive agents. But this still leaves us with the dosage problem. But this may be less formidable than anticipated because as Billingham points out there are two different dosage threshold requirements for tolerance induction on the one hand and sensitization on the other. The lower threshold for tolerance induction may be in fact very small.

One of the most important problems in transplantation immunology pertaining to the induction of tolerance is concerned with the nature and biologic significance of the transplanted antigens. Our present knowledge of this is very rudimentary. But it is not difficult to imagine that antigenic material may one day be prepared in large amounts from different human cell lines propagated in vitro. Typed "antigen" might then be available to induce tolerance of appropriately matched organ homografts in patients.

A variety of possible means of improving the effectiveness of immunosuppressive agents to promote the induction of tolerance are currently receiving much attention.[1] These include thymectomy, splenectomy, reduction of the recirculating small lymphocyte population of the body. This last can be accomplished by placement of a cannula in the thoracic duct, by local irradiation of the blood stream by means of a cartridge containing radioactive yttrium or strontium suspended in a major vessel. Another method is by extracorporeal irradiation of the blood as it passes through an arteriovenous shunt. Then there is the method of administering an antiserum produced in an alien species to the lymphocytes of the organism.

We must not forget finally that the antigenicity of the graft in some way not yet discovered may also be reduced or eliminated.

L.H.N.

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Principles Underlying The Treatment Of Obesity

There are certain things that need to be known by the physician who advises an obese patient to reduce weight. Endocrine abnormalities are rare but hypothryoidism, hyperadrenocorticism, and in the male, hypogonadism, should be ruled out as

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should fluid retention. Dietary habits need to be investigated thoroughly together with familial, economic and psychologic backgrounds. Patterns of hunger and satiety need to be understood when a patient is on a reducing diet for these form the basis of decisions on the division of the calories allotted to the reducing diet among the proper number of meals and snacks and of decisions on the eventual use of anorexigenic agents, dosage and time of administration.

The fundamental fact is that there must be established a caloric deficit by diet and exercise. It is obvious that a correct diet must be less than the accustomed intake and must provide all necessary nutrients other than calories in sufficient amounts. It must be palatable, easily available from the point of view of economics and convenience, but it must have the desired caloric deficit. Ideally, the diet must be such as to help in the re-education of the patient.

Practically every obese patient has already gained his weight which is stable when he consults his doctor. If he eliminated from 400-500 calories per day from his diet it will lead to 3,500 calories less in a week and one pound. The ease with which 500 calories can be removed daily from a diet without altering its basic structure to which the individual is adapted, should be clarified for each patient. There should not be any faster loss unless there is an especially pressing need. A busy ambulatory patient should not be obligated to tolerate a caloric intake of less than 1,500 per day and if stepped up activity is added, food intake may not even need to be cut very much.

Next is the recognition of what number of calories the patient consumes to maintain his weight, This is easily accomplished if the patient brings in a diary of his total food intake per day thus allowing the physician to clarify for the patient where the calories can be cut without basically altering the structure of his diet. Determining the caloric content of the diet is but one aspect of dietary prescription. There must be knowledge of the patient's familial and economic status, his usual eating patterns, his tastes and capabilities. This becomes obvious to the physician when he analyzes with the patient his eating diary. In short, educating the patient regarding the calorie content of various sized portions of his diet is the essential ingredient to the success not only of the weight reduction program but also of the subsequent maintenance program.

A "good" reducing diet is one on which the patient does not become too hungry. Therefore it is necessary to know the normal pattern of hunger and satiety of the patient to help decide the number of meals and snacks to prevent excessive hunger. This also is readily discerned from perusal of the patient's eating diary. One can discern when excessive hunger develops, whether frequent feedings are needed. Clearly if this does not satisfy the patient's hunger, we have a clear indication for use of an anorexigenic agent.

The current anorexigenic agents are the amphetamines and related compounds. They act chiefly by stimulating the satiety centers in the ventromedial hypothalamus. There are of course accessory actions such as stimulating spontaneous activity, releasing free fatty acids from adipose tissue, and also tachycardia, dryness of the mouth. There is little point in giving a small or moderate dose early in the morning so that its effect has worn off in the afternoon, if one is dealing with a patient who is hungry and eats and overeats in the evening. Accordingly a successful practice is to give a long-acting amphetamine preparation in the morning with a booster in the late afternoon. In general the effective duration of amphetamine therapy is of the order of a month to six weeks since it is most useful at the onset of treatment with patients who have become obese relatively recently.

Most patients do have side effects like dry mouth, restlessness, irritability, insomnia and constipation. A cardiac patient is a poor candidate for these agents because of tachycardia and possible role in potentiating arrhythmias. However, in moderate hypertension favorable effects of steady weight loss on blood pressure often outweighs the slight risk of increasing heart rate due to the amphetamines. One cannot emphasize enough that the use of such agents by the physician in no way decreases the importance of dietary prescription and instruction. The patient also needs to be warned against increasing the dose of the prescribed agent on their own or supplementing it with worthless and even dangerous over-the-counter medications.

Exercise of course is the great variable in energy expenditure which increases rapidly with the intensity with which the exercise is performed. Exercise also does not increase voluntary food intake in inactive subjects unless it reaches a critical duration and intensity.[1] It is a good idea to start an obese subject to walk every day and to increase duration and eventually the intensity of the exercise as weight reduction progresses. To build exercise into a patient's life, however, requires understanding of his schedule and mode of life. An obese person insulated by excessive adiposity will not lose heat readily on hot days and should interrupt his summer exercise with sufficient rest periods and especially to keep hydrated.

There is still too much thyroid hormone prescribed in obese patients based on a clear misconception that most obese patients are hypometabolic, a dogma that is old and untrue. This misconception arose from an old idea relating basal oxygen consumption to body weight. If hypometabolism is suspected, it is easy to settle it by a PBI or I131 uptake and need no longer be guessed at. In part, thyroid administration is self-defeating anyway since it depresses endogenous thyroid secretion which is very slow to reverse. In higher doses tachycardia, palpitation, nervousness, and insomnia appear and create an unpleasant and potentially dangerous situation. This holds true also for tri-iodothryonine.

Finally we need to be concerned with certain psychologic aspects of the therapy of obesity. We need to mitigate hunger and fatigue by spacing calorie intake to satisfy hunger. We need to fix realistic short term and long term targets. Losing weight slowly, one-half to one pound a week is more realistic for most patients and is more likely to become a permanent habit, than rapid weight loss regimens that almost always lead to relapse and weight gain.

Mayer[1] points out factors in the psychology of being obese. Experiments in patients who were obese in adolescence when the body image appears to be developed reveal a galaxy of psychiatric traits that appear to be due to the obesity—obsessive concern with the self-image, passivity, expectation of rejection, and progressive withdrawal which must be coped with if the patient is to be a happy, well-adjusted person. Many of these psychologic effects of obesity may tend to make obesity self-perpetuating and this is the reason why they are so difficult to handle adequately.

Anxiety and stress that burden an obese patient may be instrumental, especially if he is predisposed by genetics and constitution, in causing over-eating and immobilization, and hence weight accumulation. Motivation to weight reduction can sometimes be increased if a patient is informed of a newly discovered pathological condition such as diabetes, and hypertension. The development of new interests in obese middleaged women with and without anxiety can be very useful, especially women who have little to do inside or outside the home, women with too much time on their hands, and women with a tendency to view their interpersonal relations in terms of sitting down together at meals.

Clearly the obesity problem is complex and requires a knowledge of mechanisms causing hunger and satiety. How to deal with them and the psychologic aspects of obese patient is a great challenge but it needs to be done to make life longer and happier for a large segment of our population.

L.H.N.

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Can Ischemic Heart Disease Be Prevented?

The problem of arteriosclerotic heart disease and myocardial degeneration is immense. Diseases of the coronary arteries are responsible for 30 percent of all deaths among middle aged men and have been a steadily increasing cause of mortality for a number of years. Oliver[1] believes that this increase appears to be involving those under 45 at a faster rate than older sections of the population and that it is not due to improved diagnosis which has not greatly changed in the last decade. However, even if one subscribes to the view that the chief reason for the rise in prevalence of ischemic heart disease (IHD) is the greater number of middle aged people in a community resulting from a decline in mortality due to infectious diseases in children and young adults, the fact remains that IHD is a formidable medical and economic problem requiring urgent attention.

From the Framingham study[2] we learn that more than half of those who die from acute myocardial infarction do so within one hour and only just over half of those with an initial attack of acute infarction are admitted to a hospital. This high frequency of sudden death emphasizes more clearly than anything else the importance of preventing the development of IHD. But to prevent it we must know something about the causative factors and those which can be controlled.

Atherosclerosis of the coronary arteries begins in childhood or early adolescence, is present in all adults and probably progresses steadily with advancing age. In rather more than one-third of the population this leads to the clinical syndrome of IHD: angina pectoris, coronary insufficiency, congestive heart failure, sudden death. Whether or not coronary atherosclerosis will lead to ischemic heart is determined by a compound of influences including the degree and site of arterial disease, the occurrence and extent of thrombotic occulsion of the arterial lumen, the adequacy of the coronary anastomotic circulation, myocardial demands and the anatomical distribution of the coronary arteries.

The prevention of the clinical syndrome of IHD depends upon the effectiveness with which these causal factors can be controlled. Clearly nothing can be done about the anatomical distribution of the coronary arteries which may be due to genetic factors or factors operating during development

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which are as yet unknown. This leaves the problem to preventing coronary artery disease and thrombosis and of improving coronary anastomosis. Since the degree of development of each is dependent on or clearly related to the others, we must think of the three as one. As we do not as yet understand the reasons why atherosclerosis develops in children, it is unlikely that effective primary prevention will be possible for many years.

We are thus left inevitably with secondary prevention. It is secondary in the sense that arterial damage may already be advanced even though no clinical features have developed and no severe myocardial damage has yet occurred. The real focus must be on what can be done to prevent apparently healthy individuals from developing any of the syndromes of IHD mentioned above, for coronary atherosclerosis is universal in developed communities whereas fortunately IHD is not. It has been estimated that of 1,000 male doctors 40 years of age or under, 200 will develop IHD before age 65.[3] This identification of those in the population who are most at risk is important for effective prevention. Can this be done?

Many surveys Oliver points out have shown that apparently healthy individuals with the following characteristics or habits do have a greater incidence of IHD: Those with hypercholesterolemia and hyperlipidemia, those with hypertension, those who smoke cigarettes, those without any physical exercise and women with premature cessation of ovarian activity. Then there are potentially important influences such as diabetes, myxedema, psychogenic stresses, rapid weight gain, hyperuricemia and those with a thrombotic tendency.

These known risk factors are important from the point of view of prevention even when they occur singly, but when they occur in multiples they are especially important. Therefore a strong case can be made out for the elimination of as many as possible. It must be obvious that some factors are more amenable to control than others. For example searching for diabetes and properly treating it, or diagnosing myxedema and correcting it, or searching for hyperuricemia and correcting it as is now possible with allopurinol.

The prevention of the affects of psychogenic stimuli on the development of IHD seems impracticable because of the variability of an individual's reaction to a given situation. Some are overwhelmed and develop a depression. For some the same situation is a source of anxiety and for some it may be a source of enjoyment. Others behave as if the situation does not exist at all; a form of denial. Other risk factors more readily controlled.

Cigarette smoking can in theory be completely controlled. In several studies it has been well documented that mortality rates for IHD are lower among ex-smokers, than in those who continue to smoke.[4] Physical slothfulness is also potentially remediable but difficult to combat except through active education of the public to its dangers. Ovariectomy or irradiation of ovaries is sometimes avoidable and when induced or spontaneous cessation of ovarian activity has occurred prematurely, hormonal replacement is indicated and when employed is effective.

A thrombotic tendency may be as important or more so than those mentioned above. Platelet thrombi form and fibrin is deposited simultaneously leading to the accumulation of lipids in early arterial lesions and this contributes continually to their progression and to the obstructive element of advanced lesions. Preventing such a thrombotic tendency is beset with difficulties however. One is the absence of a reliable test to discover this tendency in any healthy individual. Perhaps tests of platelet adhesiveness will prove valuable. But even when such individuals are discovered there is as yet no satisfactory way of combatting a tendency to arterial thrombosis unless linolenic acid turns out to be such a substance. Since anticoagulants do not work to prevent platelet thrombi it is doubtful that their use can be relied upon to prevent arterial thrombosis. Neither has fibrinolytic therapy any part as yet to play in prevention.

As far as hypercholesterolemia and hyperlipedemia and triglyceridemia are concerned, there are several prolonged studies of diets low in saturated fats, some of which have shown a decrease and some have not. In consequence large scale long term studies of the effect of reduction in raised serum lipid levels are urgently required in those who are still asymptomatic. The "anti-coronary club" in New York[5] has shown encouraging initial results.

In summary there are two preventive approaches to IHD which should now be pressed actively and concurrently. One is to educate the public to stop cigarette smoking altogether, to avoid obesity, and for many people, to take more exercise. Such advice could emanate from the doctor's office, from health officers and through mass media. The campaign would have to be vigorous and sustained to be successful. A major shortcoming of such advice of course is that not everyone who smokes or is sedentary will develop IHD, since such an outcome will be determined by the extent and nature of three underlying pathological processes: coronary atherosclerosis, development of intra-arterial thrombosis and coronary anastomosis.

The other preventive approach is correction of hyperlipidemia especially in those who are asymptomatic, as well as searching for curable diseases like diabetes, myxodemia, hyperuricemia and forms of curable hypertension and correcting them.

We still need rigidly designed control trials in many areas especially the dietary one and we must learn much more about the thrombotic tendency.

L.H.N.

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Sympathetic Nervous System Blockers

There is growing popularity in adrenergic receptors, the reason being the recent discovery of compounds which selectively block certain cardiovascular and metabolic effects of the sympathomimetic amines. As a result the clinician now has a clearer view of the pathophysiology of many cardiovascular problems, but also new therapeutic approaches to such serious illnesses as shock, hypertension, arrhythmias, pulmonary embolism, angina pectoris and others.

A receptor is a cellular component present either on a cell membrane or inside of it which reacts with or combines with a drug. This triggers off a series of events which culminates in a specific response. An example is the blood vessel response to sympathetic nerve stimulation in which a neurohumor, norepinephrine, is released from tissue stores at or near the nerve terminal which in turn reacts with the receptor in the smooth muscle cell and initiates a series of reactions ending in muscular contraction and vaso-constriction. These adrenergic receptors can now be blocked by certain compounds termed adrenergic blockers. There are other receptors that can respond to other vaso-constrictor hormones like angiotensin and receptors responding to acetylcholine by vaso-dilatation. Neither of these are specifically blocked by adrenergic blockers.

We know since 1948 that there are two kinds of adrenergic receptors: the alpha receptor which mediates vaso-constrictor responses, and the beta receptors leading to vaso-dilatation, increased myocardial contractility and cardiac acceleration. Levarterenol stimulates the alpha receptors and isoproterenol the beta receptors. Levarterenol and isoproterenol affect the heart the same way namely, by increasing myocardial contractility and heart rate. This knowledge has come to us since the discovery of blocking agents that prevent either alpha or beta effects. An alpha blocker, dibenamine HCl, was described by Nickerson and Goodman in 1947.[1] A beta blocker, dichloro-isoproterenol, was reported by Powell and Slater in 1955. Each of these blockers is specific for its special receptor.[2]

Certain metabolic effects were then recognized as caused by sympathomimetic amines such as hyperglycemia and increase in free fatty acids which could be selectively antagonized by beta receptor blockers and not by alpha receptor blockers.[3] Important cellular effects of epinephrine such as the formation of cyclic 3′5′ adenosine monophosphate from adenosine triphosphate as well as activation of phosphorylase were also found to be caused by stimulation of the beta receptors since they could be blocked by beta blockers.[4]

An understanding of adrenergic receptors is important to the clinician since he can now select the proper vaso-pressor agent to produce a specific cardiovascular response and he can select a specific blocker to antagonize an unwanted effect. Methoxamine, vasoxyl and phenylephine predominantly produce vaso-constriction but do not increase cardiac output. They are therefore alpha-stimulators, and must be avoided in clinical situations in which an increase in cardiac output is desired, as for example, in shock.[5]

Isoproterenol (isuprel) on the otherhand is purely a beta-stimulating catecholamine. It increases cardiac output by enhanced contractility, acceleration of heart rate and it also dilates bronchioles and peripheral vessels.[5]

Then there are other amines like levarterenol, mephentermine and ephedrine which stimulate both alpha and beta receptors and may cause either vaso-constriction or vaso-dilatation.

The common alpha receptor blockers, dibenamine HC1 and phenoxybenzamine HC1 (dibenzyline) will antagonize vaso-constrictor effects. Their use has been considered in hypertension although their effects are transient. They have also been considered in treating shock where peripheral vaso-constriction is powerful and cardiac output is reduced.[6] Dibenzylene would eliminate effects of alpha receptor stimulation and its unwanted other peripheral action without interfering with the beneficial cardiac stimulating action of the beta receptors.

As one treats patients with cardiogenic or bacteremic shock with levarterenol, one often finds persisting evidence of poor tissue perfusion, cold clammy skin, cyanosis, slow capillary refill and even acidosis. Such patients are good candidates for the use of alpha blockers. They must, however, be stopped when a hypotensive response occurs and large quantities of fluid in the form of blood, dextran or Ringer lactate must be given to restore the circulating blood volume before continuing dibenzyline.[7]

In patients with pheochromocytoma before and after operation one finds high levels of circulating catecholamines that produce intense vaso-constriction and enhance capillary filtration leading to hypovolemia. Such patients could well be prepared for operation by fluid volume replacement and pretreatment with an alpha blocker, pentolamine (regitin) for 3-4 days.[8]

Among the adrenergic beta receptor blockers propranalol (Inderal) is the most potent, has the least sympathomimetic side effects and is the one available for clinical investigation and use. These blockers can lower arterial pressure by reducing peripheral vaso-constriction and might work well by reducing contractility in hypertrophic subaortic stenosis. They have also been used to prevent those cardiac arrhythmias induced by sympathomimetic amines and also those caused by digitalis.[9, 10] Patients with hyperkinetic cardiovascular states have also responded well to the administration of the beta blockers.[11,14]

Blockade of beta receptors has only a possible application in the management of angina pectoris. It requires very large doses, as much as 200-250 mg. of propranalol to cause a significant reduction in the number of anginal attacks of effort. We must recall, however, that the mechanism of action is quite complex and that such blockers interfere with the pumping action of the heart.[12] They might afford benefit to patients whose exercise capacity is limited by coronary flow and oxygen delivery to the myocardium. They, however might prove of no benefit and even harmful to those whose activity is limited by reduced pumping capacity of the myocardium.[13] When nitrites, reduced effort and an abdominal binder work there would seem to be little point in experimenting with propranalol in angina pectoris.

Potentially the list of diseases in which receptor blockage might be of beneficial effect, could expand to include almost any pathophysiologic state in which an excessive adrenergic stimulus is involved. Trials of these drugs might be anticipated in disturbances of gut motility, in excessive lipolysis or glycolysis and in attempts to modify renal excretion of cations.

In the clinical trial of these drugs, however, caution needs to be exercised since cardiac failure induced by excessive weakening of the force of heart muscle contraction is always a serious consideration.

As an investigational test, however, the blockers have helped to uncover a rich mine of pathologic, physiologic and metabolic phenomena. They have clarified our understanding of the role of the sympathetic nervous system is exercise, in postural changes, in heart failure, in shock, in arrhythmias, in thyrotoxicosis. They have allowed us to evaluate the therapeutic as well as the potentially detrimental effects of these drugs in a variety of clinical situations.

L.H.N.

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Hydrocephalus

A Review And Plea For A Vigorous Approach

James H. Salmon, M.D.* and Robert G. Selker, M.D.

■ In the early 1800's Francois Magendie described the classic clinical example of hydrocephalus of the newborn. Known to the layman as "water on the brain", Magendie speculated about such problems as where does the additional water come from, what is its composition and function and where does it go. Moreover, he was concerned with the etiology and pathogenesis of an abnormality which seemingly had no answer. Many of these questions have been solved in the intervening years. However, a number of problems remain unanswered—problems which traverse the fields of Physiology, Neurosurgery, and surprisingly enough, Philosophy.

Cerebrospinal fluid, normally produced by the choroid plexus circulates through the lateral and third ventricles, leaving the latter via the aqueduct to enter the 4th ventricle. Through openings in the lateral recesses and roof of the 4th ventricle (foramens of Luska and Magendie), cerebrospinal fluid (CSF) is permitted access to the basal cisterns and subarachnoid pathways of the brain and spinal cord for eventual absorption. The classification of Hydrocephalus is based on this physiologic circulation and is divided into three major categories: Increased production of fluid, decreased absorption, or blockage of the pathways of circulation. Communicating or noncommunicating, circulating or non-circulating are terms also applied, depending upon the patency of the pathways of circulation. The etiologies are variable and include such things as aqueductal stenosis and atresia, basal cistern arachnoiditis, Arnold-Chiari and Dandy Walker syndromes, and infrequently in infants, neoplastic lesions of the posterior fossa.

All infants with an enlarged head at birth or those whose head circumference in subsequent months increases beyond the normal percentile for other body measurements, must be considered hydrocephalic till proved otherwise. Frontal bossing of the skull, retarded motor and intellectual development, the presence of a meningocele, spread cranial sutures by X-ray and a full fontanelle, should point toward a diagnosis of hydrocephalus. Although subdural hematomas in the newborn may mimic hydrocephalus, a history of trauma or difficult delivery, parietal bossing and positive subdural taps will eventually lead to the correct diagnosis. Megalencephaly, a benign overgrowth of brain tissue, likewise must be distinguished from hydrocephalus.[1] Once suspected, hydrocephalus of the newborn must be promptly evaluated. As an in-patient, subdural taps, ventricular estimation and bubble ventriculography should be instituted to substantiate an enlarged ventricular system and the amount of cortical mantle remaining as measured in a standard brow-up view. Pantopaque ventriculography has proved a useful adjunct in delineating the site of blockage of normal flow. In addition, it seems advisable to determine qualitatively whether the hydrocephalus is of the communicating (non obstructive, circulating) or non communicating (obstructive, non circulating) variety. This is accomplished by instilling 2-3 cc of indigo carmine dye via the trans ventricular route, and observing its appearance in the spinal subarachnoid space, as well as in the urine. The latter would indicate patent absorbing pathways. If the amount of dye appearing in the urine is correlated with the time of injection, some estimate can be made with regard to the efficiency of the absorbing mechanisms.

Radiographically, hydrocephalus shows a rather discreet midline septum dividing the hemisphere and variable thickness of brain substance over the frontal temporal and occipital poles. Many authorities in the field use an average measurement of three sites rather than a single frontal pole evaluation.[2] Plain skull films rarely, if ever, show changes in the dorsum sella, rather spreading of the sutures and an enlarged fontanelle are the only significant findings. Abnormal calcification indicative of infectious diseases or congenital abnormalities may add to the etiology of the condition.

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It is at this juncture, that one's philosophy must be oriented toward a vigorous approach. Many in the past, unfortunately, some at present, feel little is to be gained by surgical intervention. Often, infants are "sent home to die" because of the seemingly "hopeless" situation. Although spontaneous arrest of progression can occur, it cannot and should not be planned for. The criteria for arrest must include the following:[3]

a.) Head measurements the same for three consecutive months.

b.) Reduction in fontanelle tension.

c.) Commencement of rapid physical, motor and mental development.

It is insufficient, we believe, to consider hydrocephalus arrested on the basis of head measurement alone. It seems reasonable and accurate to assume that at some point in the process, the brain is more easily compressed than, the skull sutures and fontanelle can be distended. Hence the skull measurements remain intact, but valuable brain mantle may be lost by compression. That cortical compression and function are directly related is evident by the stretching of the cortico-spinal tract about an enlarged ventricle with subsequent paraparesis, a theory advanced some 20 years ago.[4] Hence rapid motor and physical development *must* accompany a stable circumferential skull measurement.

In considering any surgical alteration of a clinical condition, a knowledge of the natural history of the untreated illness is imperative. In a follow-up series of 182 non operated cases, Laurence and Coates found 48.8 per cent deceased and an additional 5 per cent with progressive signs and symptoms. Two thirds of these deaths occurred before 18 months of age, less than one third lived 2 years, and a small portion died at age 5 years. Of the 46 per cent listed as living, about half were self sufficient. All but 26 of these cases, however, showed visual, intellectual, or motor problems. When calculated on actuarial principles, these authors found the chances of a hydrocephalic infant reaching adult life untreated is only 20 per cent if first seen at birth, 26 per cent if seen at 3 months, and 50 per cent if evaluated first between one and two years of age. In addition to decidedly unfavorable statistics, most every neurosurgeon has unfortunately seen the clinical end result of an untreated progressive hydrocephalic. It is the unpleasant picture of a grossly enlarged head with distended venous drainage, too heavy to be moved or turned voluntarily by the infant. Subsequent decubitae and ulceration with infection completes the picture and is the cause of death in a large percentage of cases.

In considering a patient for surgical intervention, the cortical mantle, as demonstrated by ventriculography has been used as a criteria to withhold therapy. One centimeter, and one and one half centimeters have arbitrarily been used in the past as the dividing line to predict which infant will be a future useful citizen or an institutionalized retarded child. Many authors[2,3,5] have commented on the poor correlation between mantle thickness and prognosis. Yahson, et al[2] have put forth an interesting theory which may partially answer this perplexing question. If 2 patients with hydrocephalus are evaluated, each with a 1 cm. mantle of brain—the total volume of brain tissue will not be comparable unless the head circumferences are identical. It is important therefore to take into account the total brain volume, rather than an isolated figure of 1 cm. referable to just one portion of the brain. To our knowledge no long range follow-up study has been published, correlating volume of brain with future performance.

Multiple surgical approaches have been advocated in the past. As early as 1908 peritoneal shunts[6] were reported for control of excess fluid, utilizing the absorbing potential of the peritoneal cavity. Although correct in principle, function of the shunt is plagued by failure secondary to occlusion by the omentum. Omentectomy will prolong the life of this method. In 1918, Dandy proposed choroid plexectomy on the basis of Cushings observations of spinal fluid production by the choroid plexus. In 1934 Putnam[8] recorded his experience with endoscopic cauterization of the plexus. In 1939, Torkildson[9] described his classic ventriculocisternal shunt for use primarily in obstructive hydrocephalus. This converts an obstructive hydrocephalus to the communicating variety in the hope that an adequate subarachnoid space and absorbing pathway over the hemisphere has developed. This may not be the case with infantile hydrocephalus, necessitating additional diverting measures. Numerous other surgical attempts have been described: 3rd ventriculostomy,[10] lumbar subarachnoid ureterostomy,[11] ventriculo-mastoid,[12] anterior and posterior transcallosal (from ventricle to supracollosal space)[13] ventriculo-subdural[14], ventriculo-cholecystomy,[15] ventriculothoracic duct,[16] ventriculo-ileo,[17] and many ventriculo-venous shunts.

Without doubt, the one used today with greatest frequency and best results is the ventriculo-auriculostomy of the Spitz-Holter type. Using a unique one way double valve pressure graduated system that can be pumped externally, neurosurgeons have been provided with a reliable means of controlling hydrocephalus irrespective of etiology or type. With this system, normal ventricular pressure can be maintained and the excess fluid diverted into the right heart for general systemic excretion. By virtue of the clot repelling qualities of the barium impregnated silastic tubing, as well as the intra-cardiac pressure differential and flow of blood, long-

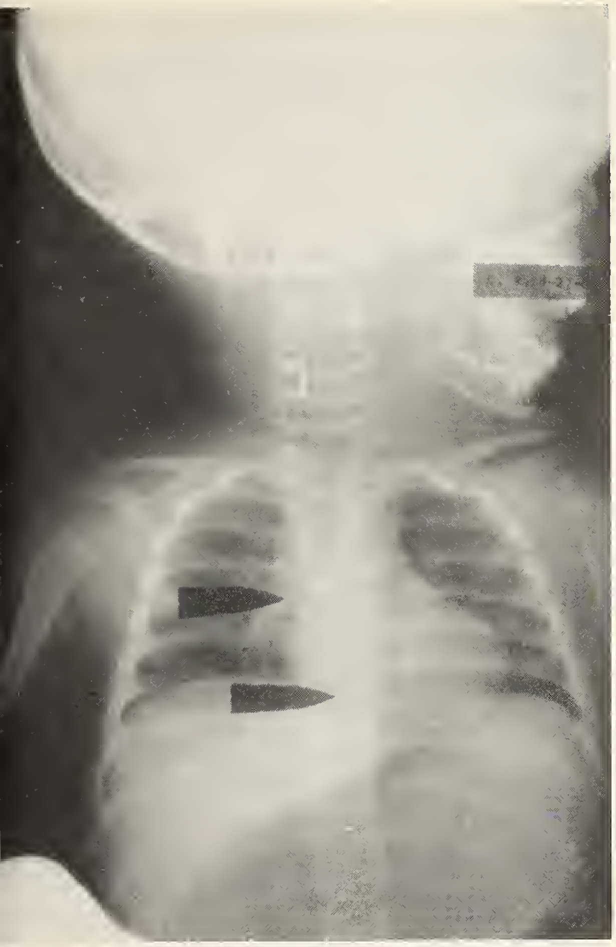


Figure I

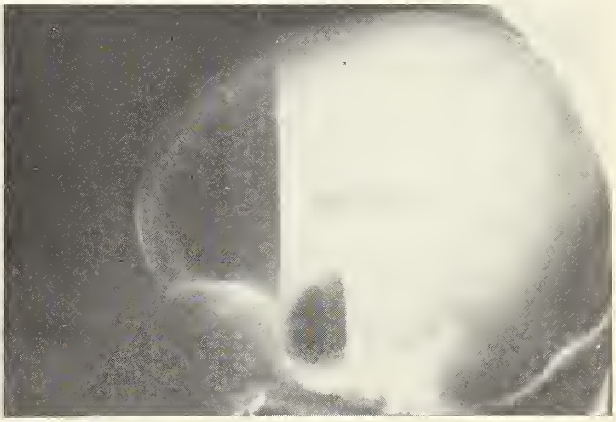
Arrows indicate desired level of cardiac catheter between bodies of $T_4$and T_6 or 7.

term, trouble-free function can be predicted. Positioned by precise EKG control,[18] the shunt procedure has become "routine" on all neurosurgical services. Once in place, the status of its function is immediately apparent by compressing the pumping mechanism. Further, particulate matter and clots which were assumed to cause the failure of previous ventriculo-venous shunts, can be forced free of the venous tubing and intracranial catheter.

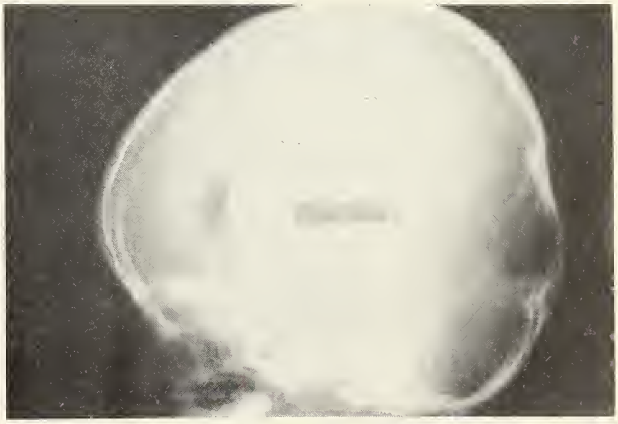
As with other man-made mechanical devices it is not always trouble-free. When placed in an infant of average size, approximately 6 or 7 cm. of tubing is required to reach from a delicate neck connection to the right atrium or the level of the T 6-7 bodies by x-ray (Figurel). As the infant grows, the distance between the connector and the right atrium rapidly enlarges, necessitating revision and replacement of the lower segment. It is apparent statistically, that any catheter lying above the T4 body is more apt to malfunction than were it below this land mark. Therefore it seems advantageous to advise *elective* revision of the shunt apparatus *before* a malfunction occurs. (Figure 2) Recanalization of venous pathways and repeated use of the same neck vein are the immediate benefits of this approach. Further as an elective procedure, the stormy events often associated with an acute blockage of the system, or a child dehydrated by vomiting secondary to an acute increase in intracranial pressure have been avoided. The brain substance has not been dealt an additional insult. The concept of *elective revision* is new, and most acceptable to parent and surgeon alike. It may indeed be the answer to the acute malfunction so commonly seen with young, rapidly-growing infants. The recent introduction of ventriculo-sagittal shunts, may answer as well, the problem of growth in the young infant.[19] Spontaneous arrest of hydrocephalus does not occur with significant frequency, once a shunt has been established.[20] Hence, the continuing need for a diverting mechanism.

Infection in the face of an intravascular foreign body can be a profound complication. Bacteremia secondary to any cause may be the etiologic agent for vegetative growth at the tip of the venous cathe-

Figure II



a) Pre-operative ventriculogram demonstrating large symmetrically diluted system.



b) Ventriculogram 17 months later at time of revision of shunt. Note increase in so called "cortical mantle."

ter with subsequent continued seeding of the blood stream, and peripheral embolic phenomena. When this occurs, immediate removal of the vascular portion of the shunt is mandatory. For this reason we believe all patients with shunts should be on prophylactic antibiotics during times of acute illness, ear infections, tooth extractions, or purulent eruptions anywhere on the body.

Other complications with this system include aseptic pulmonary emboli secondary to clot formation at the end of the venous tube, disruption of connections with loss of the tubing, thrombosis of the superior vena cava, and even cardiac perforation. Although these complications do occur, they are relatively uncommon.

Summary

A general review of the history, physiology, and surgical approaches to hydrocephalus has been presented. It is our firm belief that no patient with substantiated hydrocephalus should be denied the placement of a ventriculo-atrial shunt, even if placed only for nursing convenience. Although spontaneous arrest of hydrocephalus occurs, it must rigidly adhere to a set of strict criteria which evaluates function as well as head size. Finally, we are advocating a philosophy of *elective revision* in the rapidly growing infant, *prior* to a malfunction of the mechanical system. The complications of shunting procedures are reviewed.

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The Impact Of Alcoholism On A Psychiatric Clinic

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■ A random scrutiny of admissions to the Clinic for the month of May, 1965 revealed a significant number of patients who either had problems with alcohol themselves or whose emotional difficulties were in large measure related to alcoholism within their own family constellation.

The population served by the hospital and its clinic is approximately 200,000 people, living in an industrial city and in surrounding towns; most of these are suburban in character and many of the residents commute daily to New York. The population comprises all social classes and all levels of education and attainment. Because of the requirements of the clinic most of the patients do not come from affluent homes, although a substantial number of middle-class and upper-middle-class patients are treated because their economic circumstances have altered for the worse due to loss of employment, prolonged illness in the family or divorce with the necessity for maintaining two or more families in separate establishments.

It is, of course, difficult if not impossible to assess the number of patients in any given community who are suffering from alcoholism. Indirect methods have been used,[1,2] such as the arrest rates for drunkenness.[3] Nolan[4] in a recent report from Grace New Haven Hospital found that 13.8 per cent of 900 patients admitted to medical wards were afflicted with alcoholism. Estimates are put out by the National Council[5] on Alcoholism suggesting that there are some six and a half million people with the illness in the United States. As is the case with suicide, however, its real incidence remains as yet unknown.

It is the purpose of this paper to document the fact that, in the community served, a striking proportion of the patients are either themselves alcoholic or are closely related to an alcoholic.

In May 1965, 117 patients were seen at the Psychiatric Clinic. 19 patients (16 per cent) were suffering from alcoholism for which they were seeking assistance. 25 patients (21 per cent) were seen who ostensibly sought help for themselves for reasons unconnected with alcohol, but were found subsequently to have either a spouse or a significant relaitve whose drinking was disturbing their emotional equilibrium.

Of the 19 alcoholic patients, 9 were seen during the month in a special group therapy program for patients who had failed to respond to any other conventional approach, including A.A. The remaining 10 patients with alcoholism were seen by other staff members in either individual or group therapy. Six of them have remained sober for at least six months at the time of writing. One has been sober and in A.A. for three years.

Of the 25 non-alcoholic patients presenting with personal problems, it was found that 15 had alcoholic fathers; 9 had alcoholic mothers; 2 had an alcoholic sibling; 2 an alcoholic uncle and 7 had alcoholic husbands. 5 patients were found in whom both parents were alcoholics. It should also be noted that one third of the patients seen during May 1965 were aged between 16 and 19, in whom the incidence of alcoholism must be presumed low.

When one considers also that there are a number of other resources available in the county, including two centers of the Fairfield County Council on Alcoholism at Westport and Stamford, and two clinics especially devoted to the treatment of alcoholic addiction and sponsored by the State Department of Mental Hygiene at Bridgeport and Stamford, one may find it surprising that some 37 per cent of the patients seen in what is essentially an all-purpose type of Psychiatric Clinic have alcoholism as one of the central features of their problem.

The following case histories may give some examples of the type of problem seen.

T.W. This 20 year old girl was referred to the clinic by her family doctor. She complained of depression with intense fear of the dark and of the onset of night. She was particularly fearful of being left alone in the house. She is the second eldest of a family of eleven children and her father could be described as one of the town drunks. During her adolescent years she never saw him sober in the evening. He was frequently physically abusive to her and her siblings. He also made incestuous advances to her and her sisters. At the age of 18 she began to act out sexually, became pregnant and had an illegitimate child. Her behavior could well be understood on the basis of her father's

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actions as could her fear of night—the time when she and her sisters were exposed to her father's violence and sexuality.

H.C. This 54 year old lady has been a patient of the clinic for some four years. She is chronically depressed, has been taking Nardil 15 mgms. t.i.d. on and off for this time but she continues to work as a bookkeeper. Her husband is a retired sea captain who is seldom if ever sober. She is realistically concerned about his health. He falls down drunk and injures himself, suffers from emphysema and chronic bronchitis and is in borderline cardiac failure most of the time. She remains attached to him however and is unable to envision any kind of life without him. She is quite unable to express any anger about his drinking.

D.R. This 22 year old girl is simple and has spent most of her life withdrawing from people. She has great difficulty in holding jobs. Both her parents are alcoholics. There is a good deal of violence at home. Her mother has been repeatedly admitted to the State Hospital for alcoholism and for attempted suicide. This girl is greatly inhibited in her ability to make any kind of relationship with others. The greatest advancement made with her over a period of years has been to get her to move out of the home, take a small apartment by herself and get to work. She will probably require help for much of the rest of her life.

F.R. This attractive 39 year old woman presented with symptoms of depression and considerable anxiety. Much inquiry was required to elicit the fact that her husband was at this time serving a sentence in jail for breaking her ribs when drunk. He had been drinking heavily for many years and she was quite unable to deal with him. She had in fact lied considerably to the probation officer and the judge in an attempt to cover up for him. When he became involved with another woman she disclosed the true facts concerning his behavior and this was responsible for his being incarcerated. At the time she came for help she was expecting him to be discharged from the prison after serving six months. She was totally unable to take any stand with him or to plan for her future. She was tried in group therapy and seemed to respond quite well for a while; when she revealed her domestic situation, however, a number of the group members attempted to encourage her to be firmer. She was quite unable to tolerate this and after three months broke off treatment.

J.D. This young man has a brilliant academic record at his university. His father is a semi-skilled worker and has been alcoholic for many years, although he continues to go to his job. As a result of his father's absence and frequent drunkenness this young man has come very much under the sway of a frustrated and demanding mother and understandably has a faulty psycho-sexual identification with a great deal of anxiety and depression concerning his homosexual feelings. He has responded reasonably well to psychotherapy and at present is being encouraged to go to graduate school and move out of his parent's home.

It is not believed that this finding represents a state of affairs which is exceptional in this country. The greatest single problem in the treatment of alcoholism has to do with its detection; since the illness may flourish unseen for many years it is often difficult to gauge its impact on the patient himself, or upon those around him. On the basis of the information presented it might seem useful if those responsible for the treatment of any psychiatric disturbance were to make diligent inquiry of the patient, *and of an appropriate relative,* concerning drinking problems in the presenting individual and in the family background.

Summary

During May 1965 at the Psychiatric Out-Patient Clinic of Norwalk General Hospital, 117 patients were seen. 19 patients (16 per cent) were suffering from alcoholism and 25 patients (21 per cent) had either an alcoholic spouse or relative who was the cause of their distress. A total of 44 patients (37 per cent) were seen during the month whose emotional problems stemmed either from alcoholism in themselves or in a close relative.

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Arm Swelling Due To Venous Obstruction

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■ Venous obstruction causing arm swelling is not rare and may present in several forms. Residual symptoms are reported in many cases, and indicate that treatment must be carefully related to the circumstances of the individual patient's problem. The cases reported here represent various ways in which this condition can present and will introduce a discussion of etiology, management and prognosis.

Cases In Which Exertion Or Trauma Occurred

Case #1. Twenty-one-year-old right-handed male premedical student noted sore arm during spring baseball practice. After 10 days of symptoms sudden swelling and cyanosis of the right hand and arm occurred. Treatment within two hours with heparin, Dicumarol and elevation was instituted with progressive relief of symptoms. Venous pressure 6 years later is normal. Venous collateral pattern is not prominent. All activities are well tolerated.

Case #2. Forty-year-old right-handed law school professor and active tennis enthusiast, noted symptoms of stiffness and swelling in the right arm during a long trip on which he carried a heavy briefcase. Heparin and Dicumarol were begun one week after the onset of symptoms, and the extremity elevated. Symptoms improved but recurred about six months later, requiring a second course of Dicumarol, with improvement again noted. Minor residual symptoms five years later.

Case #3. Twenty-two-year-old right-handed male graduate student noted aching and swelling of the right arm after swimming 20 laps in the pool. After a delay of at least a week, he was seen elsewhere, a venogram performed demonstrating subclavian vein thrombosis, and physiotherapy begun. He declined hospitalization. A month later prominent venous pattern over the pectoral area and 3-centimeter asymmetry of arm circumference persisted in spite of remission of symptoms. Shoulder girdle exercises were begun. Two years later strenuous activity will still produce congestion of the arm and discomfort.

Case #4. Twenty-eight-year-old right-handed male physician developed tenderness and redness along the course of the superficial veins of the left forearm and arm after three weekends of strenuous work with a heavy wheelbarrow, pouring a cement walk. All symptoms subsided completely during elevation and therapy with Dicumarol. No residual symptoms four years later.

Case #5. Forty-five-year-old left-handed female church office worker, noted for three months gradually increasing swelling and tiring in the left hand and arm. Examination revealed the circumference of the left hand and forearm to be greater than the right, and prominent pectoral collateral vessels. Subclavian vein occlusion with a profuse collateral pattern was demonstrated by venogram. Dicumarol was given with partial improvement. Symptoms recurred whenever the prothrombin time returned towards normal. Repeat venogram showed no change in the vascular pattern. Muscle strengthening exercise for the shoulder girdle did not ameliorate the symptoms. Anticoagulants continued for nine months with incomplete resolution of symptoms. Operation was undertaken to enlarge the thoracic inlet, including division of left anterior scalene muscle, excision to the subclavius muscle and a portion of the first rib. Gradual improvement occurred in the two years since operation. There have been no further episodes of increased swelling. Slight increase in collateral venous pattern and arm circumferences, and some limitation of active use of the arm, persist three years postoperative.

Case #6. Twenty-nine-year-old male engineer, noted pain in the left upper arm after clearing stumps from a field. Two weeks later, range of motion became limited, soreness increased, an area of redness was noted, followed by a fever and chest pain. On admission to the hospital, thrombosis of the brachial cephalic and axillary veins was noted, venous pressure in the left arm was twice that in the right arm, and there was X-ray evidence of multiple pulmonary infarcts with cavitation. Hemoptysis occurred after admission to the hospital, and dyspnea increased in spite of heparin therapy. Blood cultures were positive for hemolytic Staphylococcus aureus. Ligation of the left subclavian vein was performed three days after admission to the hospital. Staphcillin was given and symptoms resolved slowly. Search for primary site of infection revealed only a questionable radiolucency of cortex of humerus, raising the possibility of osteomyelitis. Six weeks later, pain and local heat recurred, and incision and drainage revealed osteomyelitis. Nine months later sequestrectomy was performed. No evidence of venous insufficiency remained.

Case #7. Nineteen-year-old female office worker was involved in a motor vehicle accident with whiplash injury of the neck. After two weeks, swelling of the left arm and cyanosis of the extremity were noted. X-rays revealed cervical ribs, and two months after the injury anterior scalene muscle section was performed without relief of the symptoms. Venogram performed revealed no collateralization, margin of the first rib to the medial aspect of the cervical margin of the first rib, to the medial aspect of the cervical rib. No change in symptoms followed a period of muscle

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strengthening exercise. Reoperation with excision of the first rib and a cartilagenous extension of the cervical rib relieved all symptoms, and the venous pressure, which had been elevated with the arm in certain positions, decreased to normal.

Cases With No Exertion

Case #1a. Fifty-seven-year-old female had radical mastectomy for carcinoma. Osseous metastasis observed two years later and castration X-ray given. Edema of left leg noted 2½ years later, and six months before admission for hypophysectomy which was considered necessary because of uncontrolled further metastases. Recovery from anesthesia was incomplete and massive swelling from venous obstruction of the right subclavian vein and right ileofemoral veins was noted in the immediate post-anesthesia period. Expired without treatment two days postoperatively.

Case #2a. Fifty-six-year-old male incurred at different times femoral venous thrombosis and thrombosis of first one and then the other subclavian vein. Scalene node biopsy performed because of the presence of a hylar mass revealed undifferentiated carcinoma. Arm vein thrombosis occurred in spite of Coumadin therapy and was treated by Thrombolysin (Merck), heparin and Persantin. Swelling decreased on this program but pulmonary infiltrates appeared suggesting probable pulmonary embolism. Convalescence was stormy. Followup revealed progressive cachexia, although swelling of arms was minimal. Death occurred four months later.

Case #3a. Fifty-three-year-old male office worker noted swelling of the side of the neck and shoulder. Incomplete resolution following Actase therapy elsewhere. Heparin and long-term oral anticoagulants were given with near complete resolution. Angiogram revealed some extrinsic pressure displacing the subclavian vein, with radiopaque shadow in the upper mediastinum. Chest X-ray was otherwise negative, but three years later pain in the upper anterior chest on coughing occurred and X-ray revealed diagnosis of carcinoma of the lung. Venogram revealed obstruction of the innominate vein, with flow to the opposite side, nonfilling of an apical branch of the pulmonary artery. Biopsy at the time of thoracotomy revealed poorly differentiated carcinoma. Pneumonectomy was performed with extra-pleural dissection. Cerebral metastases occurred two years postoperatively and the patient died shortly afterwards.

Case #4a. Fifty-four-year-old male treated for four years with hormone therapy for prostatic cancer. Mesenteric infarction required hospitalization and bowel resection. Cephalic vein cutdown in the left upper extremity was performed preoperatively. Eight days later progressive swelling of the hand and arm was noted. Thrombolysin (Merck) was given, followed by heparin, with resolution of the swelling and return of arm circumferences to normal. Ten days later thrombophlebitis of one lower extremity occurred. The patient is now maintained on Coumadin. Short-term followup reveals no arm symptoms.

Case #5a. Eleven-year-old male sustained high-voltage electrical burns of the left hand and upper extremity, with arcing burns of antecubital, axillary, neck and heel areas. Immediate post-burn swelling of antebrachium proceeded to involve entire upper extremity with prominent venous collateral over the pectoral area. For presumed axillary vein thrombosis, heparin therapy 50 mg i.v. every four hours was begun two days after wounding. Swelling decreased progressively thereafter. Venous thrombosis was noted at subsequent debridement and reconstructive operations which were performed without any complication due to venous insufficiency.

Case #6a. Sixteen-year-old male sustained buzz saw injury across palm of left hand. Primary nerve and tendon repair required application of pneumatic tourniquet twice, totaling 3½ hours. Rapid increase in swelling of entire extremity occurred on 4th postoperative day, with prominent venous collateral pattern. Therapy begun with heparin and fibrinolysin (Thrombolysin, Merck), 8 ampules given during a forty-minute period. Euglobulin clot lysis times and released radioactivity from I^{125}-labeled human plasma assay clots[1] confirmed that a thrombolytic state had been induced. Progressive decrease in swelling was observed and at discharge arm circumference measurements were equal. Coumadin was given for one month. No evidence of venous obstruction is evident at followup examination.

Discussion

The etiology of swelling from venous obstruction in the arm is often apparent at the time of initial examination. A history of effort or unusual exertion was present in one-half of the cases reported here, and when this history is obtained it serves to separate the cases into one of two groups. Although initial treatment is similar in both, the prognosis is somewhat related to etiology and therefore it is of practical importance to determine whether extrinsic pressure on the vein at the thoracic inlet is a factor. In general, vein obstruction from extrinsic pressure is much less likely to present the risk of pulmonary embolism. This can be understood, if one considers the fact that if extrinsic pressure causes subclavian vein thrombosis, periphlebitis is likely to result in secure fixation of the thrombus within the vein. Furthermore, narrowing of the vein amounts, for all practical purposes, to partial ligation of the vein. Under these circumstances, embolism is unlikely, but the collateral venous drainage may not be adequate to obviate later edema and persistent symptoms. When subclavian vein thrombosis is not due to extrinsic pressure at the thoracic inlet, embolism is definitely more of a hazard. Pulmonary embolism was noted in 42 per cent of Loring's collected series of cases having congestive heart failure.[2] Vein ligation is clearly indicated when suppurative thrombophlebitis is present in the extremity, as in Case #6. Though this is an uncommon situation, it may be noted that the first clinical description of thrombophlebitis by Hunter, and the concept of vein interruption postulated by him (in the form of extrinsic pressure), were related to such a case.[3] The widespread current practice of using polyethylene tubing for intravenous therapy by cutdown and intracatheter techniques presents some risk of suppurative thrombophlebitis. Careful skin preparation and the prophylactic use of topical antibiotics appear to be justifiable precautions.[4,5]

Vein ligation may be indicated following pulmonary embolism if the embolus occurred in spite of adequate anticoagulant therapy. When thrombophlebitis in more than one area is present, as in the case #2a, it may not be obvious which venous pathway to interrupt, however. In this situation anticoagulant therapy must be continued, whether or not vein ligation is done.

Under any other circumstances than suppurative thrombophlebitis, anticoagulant therapy should be instituted as soon as the diagnosis is apparent. If the interval since the onset of symptoms is less than 48 hours, thrombolytic agents can be considered. A full discussion of the effectiveness of this modality is beyond the scope of this paper, but with effective agents and proper laboratory control, the treatment seems logical. Current literature is available which describes the present status of treatment with thrombolytic agents.[6]

Adequate anticoagulant therapy consists of intravenous heparin given at intervals. Fifty milligrams every 4 hours is preferred, though in a given case lack of response to therapy may indicate that larger doses should be used. The dose in these cases should be individualized, as Thomas has recently reemphasized.[7] At the same time, the arm should be elevated to decrease swelling and increase the speed of flow in venous collaterals. Serial measurement of the venous pressure and of limb circumferences at several points should be made to provide an index of the effectiveness of treatment and the adequacy of collateral veins. Venous pressure during and after exercise, such as fist-clenching, provides a further test of the adequacy of collaterals. Satisfactory response to initial treatment with anticoagulants (and possibly thrombolytic agents) should be apparent in the first few days. If the process fails to resolve or the diagnosis is unclear, venography is indicated. Serial venograms may be used to follow the progress of treatment.

Operation to enlarge the thoracic inlet should be considered if swelling does not resolve progressively. Ofston and Merendino have reported that operation will relieve swelling.[8] The decision concerning operation should not be long delayed if the process is of recent onset. In Case #5, over 7 months had passed before operation was undertaken. At operation, narrow segment of fibrotic and recannalized subclavian vein was found which did not expand when the thoracic inlet was enlarged by dividing the anterior scalene muscle and removing the subclavius muscle and a part of the first rib. Continued gradual improvement since operation is as likely due to continued improvement in collateral circulation as to the procedure, in this case. A better result might have occurred if decision to operate could have been made earlier in the course of the disase. An immediately good result was observed in Case #7, postoperatively, which may be attributed to the fact that thrombosis of the subclavian vein had not yet occurred. In this case scalene muscle section alone was not adequate to enlarge the inlet space.

If the result of early treatment is satisfactory, certain further measures are indicated. Oral anticoagulants appear to be indicated for a month or more to prevent extension of thrombosis in the essential collateral vessels. Two of our cases, #2 and #5, had several courses of prothrombinopenic drugs which were begun in each instance because of recurrent symptoms consisting of swelling of the arm and a feeling of stiffness. These symptoms ameliorated when the prothrombin time was depressed. The reason for this improvement is not entirely clear, because serial venograms did not demonstrate that there was new thrombosis in collateral veins. Nevertheless, the impression is gained that residual symptoms of venous obstruction seem to respond to additional therapy with Coumadin, and in general, cases given Coumadin for a month or longer as part of the initial therapy had the fewest residual symptoms.

Muscular exercises prescribed have the purpose of altering posture from depression of the shoulder girdle to elevation and protraction. The exercise is carried out from a position of mid-elevation of the shoulder girdle. From this position, weights are lifted to strengthen the muscles elevating the shoulder girdle. The exercise is not carried out in the lower half of the range of shoulder girdle motion.

Residual symptoms in cases where effort or exertion have not been noted in the history are presumed to be due to extensive obliteration of the major venous and collateral pathways. In such cases it is more difficult to predict that operation to enlarge the thoracic inlet will relieve the symptoms. Physical measures for managing chronic venous insufficiency are appropriate, including elevation of the extremity at night, physical therapy, moderate limitation of the use of the extremity to the extent that large demands for arterial inflow related to intermittent vigorous exertion are avoided, and external compression may be applied if symptoms warrant. Swelling rarely leads to skin complications in the upper extremity because the venous pressure is never as high as when venous insufficiency occurs in the lower extermities, but it may be unsightly and it may interfere with work. In none of the cases reported here did swelling require compression by elastic garments or pneumatic devices.*

Venous thrombosis occasionally, though rarely, presents as the first evidence of an otherwise unsuspected neoplasm. One such case, #3a, was noted here, and in another, #2a, bilateral arm vein thrombosis occurred. Local factors may influence the site of venous thrombosis in these and other cases. Arm vein thrombosis occurred after scalene node biopsy in Case #2a and has been reported by others.[9] Cephalic vein cutdown in Case #4a probably influenced the site of thrombosis in this patient who had disseminated cancer and venous thrombosis elsewhere. Position of the arm at the time of surgery and the use of the pneumatic tourniquet could be implicated in Case #6a. High-voltage electric burns may be followed by vascular complications because blood vessels are the best conductor in the electrified extremity.[10]

Limited experience with tests performed on the blood to detect a "hypercoagulable" state[11] indicate that when a history of effort is elicited the test results are normal. In some cases in which there is no history of effort the tests have indicated a thrombotic tendency in the blood. This has been noted especially in the presence of cancer.

Summary

Swelling due to arm vein obstruction presents a problem in diagnosis because it is uncommon, but should be easily recognized from pronounced venous collateral pattern, arm measurements, and elevated venous pressure, and is confirmed by venography. A history of effort or exertion tends to classify the individual case as being primarily related to extrinsic pressure at the level of the first rib. In this circumstance, pulmonary embolism is virtually unknown, but residual symptoms may be troublesome if treatment is delayed. Anticoagulants are advisable, thrombolytic agents if the process is recent, and operation should be undertaken if symptoms do not subside promptly. If no history of effort is elicited, the process is more likely to be related to a thrombotic diathesis, such as may be associated with cancer or heart failure. Pulmonary embolism is a definite possibility, but treatment with anticoagulants and thrombolytic agents, if applicable, may yield a good result.

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* Excellent equipment of this type is manufactured by the Jobst Company of Toledo, Ohio, from patterns and to degrees of compression prescribed by the physician.

Insulin Antagonism, Resistance, And Inactivity

Henry G. Hanley, M.D.

■ The biological effectiveness of a given amount of insulin, whether exogenous or endogenous, may be altered by many processes which operate at tissue enzyme, cellular, and plasma levels. Much has been done to elucidate the nature of these processes in recent years, and many speculations have been made as to the clinical importance of each process following its discovery. It has become increasingly evident that more work needs to be done before a valid assessment can be made of the relative importance of the various mechanisms now known to exist, and this paper will stress the nature, rather than the clinical importance, of the processes leading to altered biological effectiveness of insulin.

Enzymatic Processes

One of the first processes to be publicized was the degradation of insulin by insulinase. Insulinase was first isolated in 1949 by Mirsky and Broh-Kahn[1,2] from rat liver. It is a proteolytic enyzme[3-5] and is extremely potent. Rat liver insulinase can degrade 0.5 units of insulin/gm./min.[6,7]. The role of insulinase has not been fully elucidated. It may be involved in normal regulation of insulin activity[8,9], but speculation about possible alterations in its activity in diabetes mellitus are tenuous at best, as studies with I-131 insulin have shown it to have a normal half-life in diabetics[10].

Another enzymatic process that causes the degradation of insulin was described in 1958 by Tomizawa and Halsey[11]. They isolated a second enzyme from beef liver which degraded I-131 insulin. Their work was extended by Katzen and Stetten[12], who showed that this enzyme catalyzed the reduction of the disulfide bonds of insulin by glutathione. It was called hepatic glutathione- insulin transhydrogenase. The sequence of reactions necessary for the degradation of insulin requires TPNH. This sequence consists of: First, oxidation of TPNH by glutathione in the presence of glutathione reductase, and second, the reduction of insulin by the reduced glutathione in the presence of glutathione-insulin transhydrogenase. As with insulinase, the importance of this system is not clear at the present time. (Figure 1)

FIGURE I

$$\text{TPNH} + \text{Glutathione} \xrightarrow{\text{Glutathione Reductase}} \text{TPN}^+ + \text{Reduced Glutathione}$$

$$\text{Reduced Glutathione} + \text{Insulin} \xrightarrow[\text{Transhydrogenase}]{\text{Glutathione-Insulin}} \text{Reduced Inactive Insulin}$$

Cellular Processes

Very little is known about the mechanisms by which an intrinsic cellular resistance to insulin may take place, if it occurs at all. It has been postulated to occur in rare instances. Field, Johnson, and Herring[13], and Tucker, et al.[14] have reported two cases in which insulin resistance seems, by exclusion, to be at a cellular level. Both the patients had acanthosis nigricans. They showed extreme insulin resistance, and despite extensive testing, no insulin antagonist could be found that would account for this. This is negative rather than positive evidence for intrinsic cellular resistance however, and there is no explanation of how this resistance takes place, if it does occur.

Plasma Processes

Those processes occurring predominantly in plasma are divided into those associated with hormones, those associated with plasma insulin antagonists, and those associated with bound or "atypical" insulin.

Hormonal Antagonism To Insulin

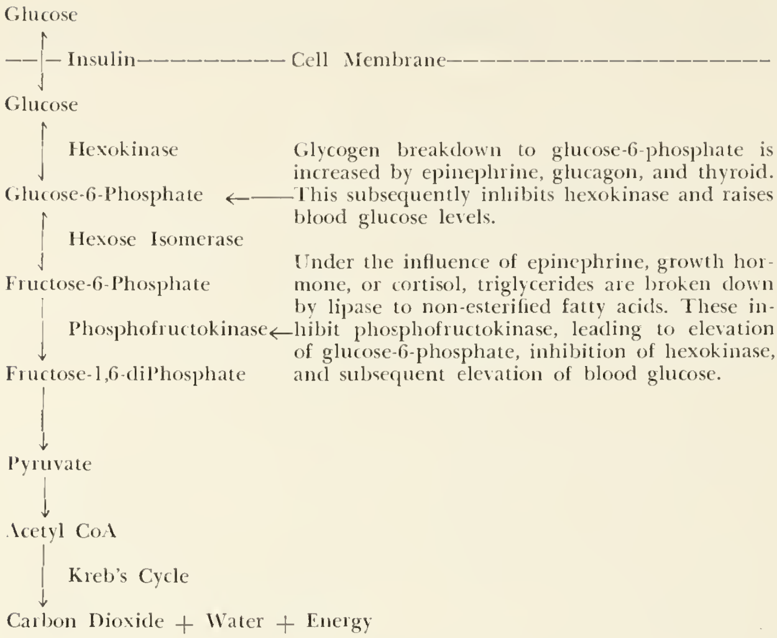
Growth hormone, the glucocorticoids, epinephrine, and thyroxine all exhibit varying degrees of anti-insulin activity. Their mechanisms of action are somewhat different.

All the mechanisms of action of growth hormone are not fully understood at the present time. It may cause the liberation of an insulin antagonist from the pancreas.[15] In addition, growth hormone has an adipokinetic effect,[16] raising blood concentrations of non-esterified fatty acids (NEFA). High NEFA levels inhibit phosphofructokinase, which depresses the glycolytic rate, and causes the accumulation of glucose-6-phosphate (Figure 2). Finally, high levels of glucose-6-phosphate inhibit hexokinase, and this limits glucose uptake by the cell.[17] A third locus where growth hormone may have a role is in the control of the pituitary dependent synalbumin insulin antagonist of Vallance-Owen,[18] to be discussed later in this paper.

DR. HENRY G. HANLEY, intern, Boston University Medical Service, Boston City Hospital, Boston, Mass.

Figure II

Utilization of Glucose



Glycogen breakdown to glucose-6-phosphate is increased by epinephrine, glucagon, and thyroid. This subsequently inhibits hexokinase and raises blood glucose levels.

Under the influence of epinephrine, growth hormone, or cortisol, triglycerides are broken down by lipase to non-esterified fatty acids. These inhibit phosphofructokinase, leading to elevation of glucose-6-phosphate, inhibition of hexokinase, and subsequent elevation of blood glucose.

Epinephrine may oppose insulin in three ways. When glycogen is present in the liver, epinephrine stimulates its conversion to blood glucose.[21] Epinephrine also causes muscle glucose-6-phosphate levels to rise, secondarily leading to inhibition of muscle hexokinase which limits glucase uptake.[22, 23, 24] Finally, it increases the activity of lipase raising blood free fatty acid concentrations,[25] and in this way may inhibit hexokinase similar to the action of growth hormone.

Thyroxine leads to both increased glucose production by the liver[26] and increased utilization of carbohydrate in the periphery.[27] The net result provides no uniform opposition to insulin action.

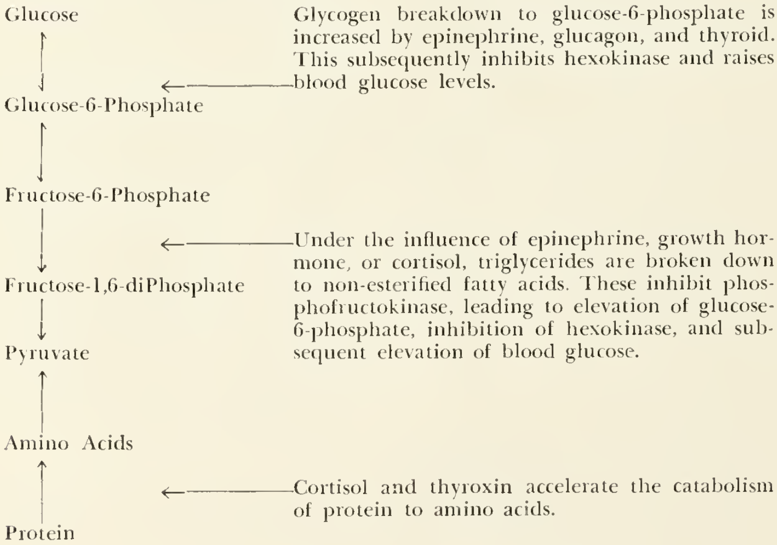
The adrenal cortical hormones oppose insulin action mainly by increasing gluconeogenesis from protein (Figure 3). They also appear to have an effect in decreasing glucose utilization by extrahepatic tissues.[20]

Other Plasma Insulin Antagonists

Insulin binding antibodies were described in the literature in sporadic reports in the 1940's,[28, 29, 30] but did not come into their present prominence

Figure III

Glucose Metabolism in the Liver Cell



Glycogen breakdown to glucose-6-phosphate is increased by epinephrine, glucagon, and thyroid. This subsequently inhibits hexokinase and raises blood glucose levels.

Under the influence of epinephrine, growth hormone, or cortisol, triglycerides are broken down to non-esterified fatty acids. These inhibit phosphofructokinase, leading to elevation of glucose-6-phosphate, inhibition of hexokinase, and subsequent elevation of blood glucose.

Cortisol and thyroxin accelerate the catabolism of protein to amino acids.

until 1956 when Berson, et al. showed that beef-pork mixtures of insulin are uniformly antigenic, and that insulin binding antibodies are present in virtually every diabetic patient treated with insulin for more than a few months.[10] They have never been shown to be present in a person not previously treated with insulin.[31] The reason they are not more of a problem in causing clinically significant insulin resistance in the vast majority of patients is that usually they are only present in sufficient quantity to bind 5-10 units of insulin per liter.[10,31,32] In the rare patient in which high levels develop, they may cause extreme resistance to insulin. The insulin binding capacity may rise above 1000 units per liter,[31] causing high clinical resistance. Also, as existing antibodies are forming complexes with insulin, new antibodies are being synthesized, leading to a chronic requirement for high doses of insulin. Since their discovery, the insulin binding antibodies have been shown to migrate electrophoretically between the "β" and "γ" globulin fractions, and to form two types of complexes with insulin.[32]

The next insulin antagonist to come into prominence was discovered by Bornstein and Park in 1953.[33] They found that the serum of alloxan diabetic rats contained an inhibitor of glucose uptake as measured by the rat diaphragm bioassay. This inhibitor reduced diaphragm uptake of glucose in vitro by approximately 25 per cent. Adrenalectomy or hypohysectomy of the diabetic animals resulted in the disappearance of inhibition. This inhibitor was subsequently recovered from the β_1 lipoprotein fraction of the serum.[34] It appears to be regulated by but distinct from growth hormone as: 1) Growth hormone in vitro causes no inhibition of glucose uptake by the rat diaphragm, whereas this serum factor does inhibit uptake in vitro, and 2) Growth hormone in vivo has a latent period of several hours. The factor just described does not have a long latent period.

In 1956 Field and Stetten discovered a humoral antagonist to insulin in human sera that appeared during the stage of acute diabetic acidosis and disappeared within a short while following therapy.[35] Measurements were made by the rat diaphragm bioassay. The inhibitor was subsequently shown by them to be a non-lipoprotein with the electrophoretic mobility of an α_1 globulin.[36]

The antagonist currently receiving the greatest attention is the synalbumin antagonist discovered in 1958 by Vallance-Owen.[37] It was first noted that an insulin antagonist was associated with the albumin fraction of the plasma. The antagonist was present in the plasma of both diabetic patients and normal individuals, but was two to four times more concentrated in the plasma from the diabetics. The antagonistic factor was subsequently separated from the albumin fraction,[38] and since then it has been more extensively studied. The following observations have now been made: Synalbumin prevents the action of insulin on glucose uptake by the rat diaphragm in vitro but does not affect the activity of insulin in increasing glucose uptake by adipose tissue. The reason for this discrepancy between results obtained with muscle and fat has not been fully explained. The antagonistic activity disappears following adrenalectomy or hypophysectomy.[40] Besides diabetics, higher levels of synalbumin have been found in asymptomatic relatives of diabetics and a high percentage of patients who have suffered myocardial infarctions.[18] The inheritance of high synalbumin antagonist levels suggests a dominant genetic trait. There is now evidence to suggest that synalbumin may be the "B" chain of insulin itself.[41] (Insulin is formed by two chains, called the "A" and "B" chains. The "B" chain has 30 amino acids and is connected to the "A" chain by disulfide bonds.) This discovery has led to much speculation on the role of a degradation product of insulin in clinical diabetes mellitus,[18] but thus far its importance has not been determined.

Finally, in 1960, Vargas[42] studies normal human plasma and found that the α_2 and β globulin fraction inhibited glucose uptake by the rat diaphragm in the absence of insulin and masked the effects of the insulin-like activity present in the α_1-albumin fraction.

Bound And Atypical Insulin

Bound insulin was first described by Antoniades in 1961.[43] His studies indicate that a fraction of endogenous insulin is bound to a basic protein, and that this bound fraction is active by bioassay on the rat epididymal fat pad but not on the rat diaphragm. The proposed significance of this is that if a substantial amount of insulin is present as circulating complexes, and if these complexes dissociate following glucose administration, then the defect in some diabetics might be that the complexed insulin dissociates at a slower rate in response to glucose administration.[44] Berson and Yalow have examined this work[31] and have found several inconsistencies. Further studies relating to the presence and significance of bound insulin are needed.

Atypical insulin is defined as insulin-like activity as measured by the rat epididymal fat pad bioassay that cannot be neutralized by potent insulin antiserum.[45] Activity of this type persists in dogs after total pancreatectomy,[46] is found in crystallized serum albumin, and is even found in egg albumin.[31] The substance responsible for this activity has not been well characterized.

Summary

The biological effectiveness of a given dose of insulin may be altered by many factors. Among those now known are tissue enzymes, hormones and insulin antagonists in plasma, an insulin binding protein, and an atypical type of insulin activity. The possible role these substances play in the regulation of insulin metabolism in the normal and diabetic individual awaits further investigation.

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PHYSICIAN-PATIENT RAPPORT

The importance of first impressions is often overemphasized, but it must never be overlooked. The patient may be watching you closely. Your general appearance, your dress, your actions, your attitude, your words and even the tone of your voice will all have an effect, favorable or otherwise. You may have seen an experienced physician attempting to size up the patient as he approaches the bedside; he will vary his opening remarks in accordance with this first impression. It is usually advisable to rely upon a simple introduction in a friendly tone such as: "Mr. Jones, I am Dr. Smith." Hesitate, watch the patient, and try to take advantage of any remarks he may make. Forget momentarily that you're the doctor and he is the patient; be sociable, as you would with any other stranger. At a propitious moment you can continue with some remark such as: "Now tell me all about your troubles." Never ask him what his "symptoms" are. Don't ask: "What's wrong with you?" or "What brought you here?"; that is what he wants you to tell him. Just give him an opportunity to talk and to tell his story in his own way.—H. U. Hopkins, M.D., Ed., *Leopold's Principles and Methods of Physical Diagnosis. Third Edition.* 1965, pp. 2-3.

Evaluation And Selection Of Candidates For Surgical Intervention In Acquired Mitral And Aortic Valvular Disease

Allan V. N. Goodyer, M.D. and William W. L. Glenn, M.D.

■ The decision to bring a patient with valvular heart disease to cardiac surgery depends on accurate assessments of the extent and prognosis of the patient's disability, and of the likelihood of survival and benefit from surgical intervention. These evaluations are made particularly difficult by wide individual variations in the natural history of valvular heart disease and in the impact of cardiac impairment on each patient's way of life, as well as by rapid developments in the field of cardiac surgery itself. Nevertheless, it is possible to formulate guidelines which apply to present selection practices, and which should also provide the basis for revised attitudes in the near future.

A. Evaluation

Evaluation of a patient with valvular heart disease for cardiac surgery involves three steps: 1) detection of a "significant" organic valve lesion; 2) determination of the severity of the lesion, and its relevance to the patient's disability; 3) comparison of the estimated medical and surgical prognosis with regard to both mortality and morbidity. These steps will now be considered in more detail:

1) DETECTION

Most patients with mitral or aortic valvular heart disease of sufficient severity to raise the question of cardiac surgery have a murmur, electrocardiographic or radiographic evidence of cardiac enlargement or hypertrophy, and syncope, congestive failure, or progressive exertional dyspnea or angina with mild forms of ordinary activity (Class III according to the New York Heart Association classification). Occasionally, surgery must be considered in patients who ordinarily have minimal or no symptoms, but who present with sudden hemoptysis, pulmonary edema, or peripheral embolism.

2) DETERMINATION OF THE SEVERITY OF THE LESION

Where symptoms interfere with the patient's ordinary way of life, and are not easily controlled by good medical management, the possibility of surgical treatment must be considered. Further evaluation is then in order, with the following aims: a) to identify the major valve lesion, particularly in cases of multivalvular involvement; b) to grade the severity of the resulting hemodynamic impairment in order to provide a basis for explaining the patient's symptoms and for estimating a medical and surgical prognosis; c) to identify other causes of cardiorespiratory impairment, such as pulmonary parenchymal or embolic vascular disease and myocardial failure with or without coronary vascular disease; and d) to uncover special features such as valve calcification which are of particular interest to the surgeon.

Table I summarizes the key objective auscultatory, electrocardiographic and radiologic findings which usually bespeak severe valve lesions, and which, in the symptomatic patient, warrant further special studies. Frequently, these data provide a better index of the stage of a patient's disease than do his symptoms. Table II summarizes the findings at cardiac catheterization and angiocardiography which are of particular importance in evaluating the severity of mitral and aortic valve lesions, and the secondary consequences thereof. These tables deal with individual valve lesions. Unfortunately, rheumatic heart disease is frequently multivalvular, and even mild lesions may have a bearing on the prognosis of another more major valve impairment. It is important, therefore, to identify minor as well as major valve lesions, and particularly to warn the surgeon regarding even minor aortic regurgitation, if an "open" procedure on the mitral valve is contemplated, since retrograde flooding of the mitral operative field may then require intermittent aortic cross-clamping, with attendent increased operative risk. Table III summarizes the intracardiac pressure measurements in 37 patients with predominant aortic stenosis or mitral regurgitation in whom these data were available prior to

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Presented, in part at the Cardiovascular Symposium of the St. Francis Hospital, Hartford, Connecticut, May, 1966.

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Table I
Key Objective Signs of Severe Valve Lesions

LESION	PHYSICAL EXAM.*	RADIOLOGIC EXAM.*	ECG*
Aortic Regurg.	Long, loud murmur Collapsing pulse Low diastolic blood press. S_3 gallop	LV enlarged Aortic pulsation	LVH
Aortic Stenosis	Harsh, radiating murmur Thrill; LV thrust Diminished S_2 Prominent S_4	Valve calcified (heavily) Post-sten. aortic dilatation LV enlarged	LVH LAH
Mitral Regurg.	Long, radiating murmur LV lift Wide S_2 split, obscured M_1 S_3 gallop	LV & LA enlarged Abn. pulm. vasc. pattern	LVH or/and RVH
Mitral Stenosis	Long, loud murmur RV lift Loud M_1& P_2 Short S_2-OS (.06-.09)	Valve calcified (heavily) Abn. pulm. vasc. pattern LA enlarged	RVH

* LV = left ventricle
LVH = left ventricular hypertrophy
RV = right ventricle
RVH = right ventricular hypertrophy
LA = left atrium
LAH = left atrial hypertrophy
S_2, S_3, S_4 = heart sounds
S_2-OS = interval between second heart sound and opening snap
M_1 = first sound at apex

valve replacement at this institution. The mean left atrial pressure was usually near normal in the patients with predominant aortic stenosis, but other average pressures were similar to those of patients with predominant mitral regurgitation. Right ventricular failure was usually absent, but some degree of pulmonary hypertension occurred in every case of mitral regurgitation and in about half the cases of aortic stenosis.

Table II
Findings at Cardiac Catheterization with Severe Valve Lesions

CATH. FINDINGS‡	AORTIC REGURG.	AORTIC STENOSIS	MITRAL REGURG.	MITRAL STENOSIS
Valve area		1 cm^2		1 cm^2
LVEDP	18	15	15	
LAP (mean)			20	20
PAP (syst.)	45	45	55	55
P. Vasc. Res.	6	6	7	7
RVEDP	7	7	8	8
Regurg. vol.	3-4 +		3-4 +	

‡ LVEDP = left ventricular end-diastolic pressure (mmHg)
LAP = left atrial pressure (direct or "wedge") (mmHg)
PAP = pulmonary artery pressure (mmHg)
P. Vasc. Res. = pulmonary vascular resistance $\left(\frac{\text{PAP-LAP}}{\text{card. output}}, \frac{\text{mmHg}}{\text{liters/min.}}\right)$
RVEDP = right ventricular end-diastolic pressure (mmHg)
Regurg. vol. — angiographic estimate of degree of regurgitation on a scale of 1+ (minimal) to 4+ (heavy) opacification of chamber proximal to defective valve.

3) COMPARISON OF MEDICAL AND SURGICAL PROGNOSIS

The course of valvular heart disease under medical management is quite variable, but a rough guide of longevity is provided by several studies[1-5] summarized in Figures I and II. In addition, some non-rheumatic diseases (Table IV) produce valve lesions which cannot be considered in the same way as the rheumatic or calcific (aortic) lesions which provided the data for Figures I and II. For instance, when aortic regurgitation due to trauma or bacterial endocarditis causes rapidly progressive ventricular failure, the valve must be quickly replaced, even though the operative risk is high. An atrial myxoma should be removed when identified, even with mild symptoms. On the other hand, repair or replacement of a mitral valve which is re-

Table III
Intracardiac Pressures and Other Features of 37 Patients prior to Starr Valve Insertions*

	NO.	MAIN LE-SION	AGE	CLASS‡ (I-IV)	LAP MEAN	PAP SYST.	EDP LV	EDP RV	ΔP§ VALVE
av.	23	MR	44	III	23	56	12	7	
range			23-55	III-IV	15-33	31-95	5-30	2-17	
av.	14	AS	48	III	14	46	16	7	75
range			19-65	III	5-39	18-82	7-40	3-13	54-121

* Abbreviations of Tables I and II. Pressure values in mmHg.
‡ Classes I-IV of NY Heart Association classification.
§ ΔP = pressure difference across valve.

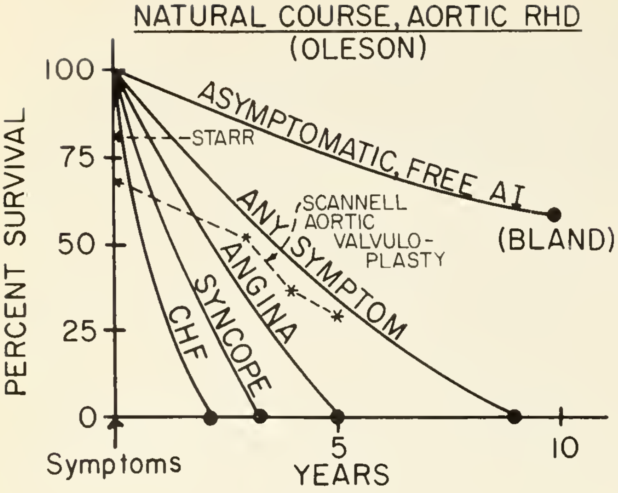

Figure I

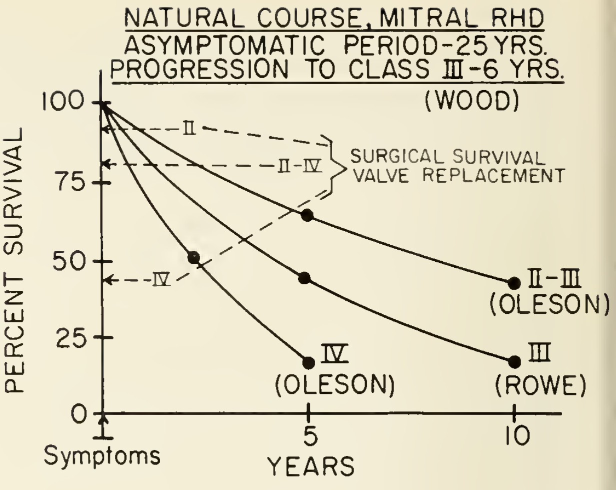

Figure II

gurgitant due to myocardiopathy is unlikely to improve cardiac function.

The data in Figures I and II indicate that survival is conditioned by the severity of the disease, and by the leading symptom manifested. Comparable data on patients treated by surgery are not available, but there is considerable evidence that survival is extended and morbidity much reduced by "closed" mitral commissurotomy (using a dilator) in cases of essentially "pure" mitral stenosis particularly when radiologic examination including cinefluoroscopy discloses no more than a trace of calcification of the valve.[6,7] Although recurrence of disability leads to mortality or reoperation at the rate of about 5 per cent per year the good results of the "closed" operation favor its continued use for predominant mitral stenosis until the safety and long-term efficacy of valve replacement have been demonstrated. In some centers, where the results from "closed" commissurotomy have apparently not been considered satisfactory, "open" valvuloplasty (using a dilator and dissection under direct vision) has replaced the "closed" procedure.[8,9] Unquestionably, in some cases "open" valvuloplasty will provide a more complete correction of mitral stenosis than "closed" commissurotomy. In our experience, however, the "closed" procedure performed with a dilator[10] has provided in nearly all cases a widely open mitral valve without producing regurgitation and at an operative mortality of only about 1 per cent vs. 6-9 per cent for the "open" procedure.[8,9,11] "Open" debridement of the aortic valve, which probably improved longevity in one series[12] (Figure II), has been almost entirely superseded by prosthetic valve replacement except in young patients with congenital aortic stenosis who usually have a better prognosis than adults with comparable lesions, and in a few adults without valve calcification.[13,14] Early results with replacement of the mitral or aortic valve are encouraging, but no adequate long-term comparisons with medical management are yet possible. The poten-

Table IV
Non-Rheumatic Valve Lesions with Special Implications for Valve Surgery

DISORDER	LESIONS*
Subacute bact. endocarditis	AR
Carditis & cardiomyopathy	AR, MR
Cardiamyopathy (hypertrophic)	"AS", MR
Aortic medionecrosis & aortitis	AR
Trauma	AR, MR
Ruptured pap. muscle or chorda	MR
Cardiac aneurysm	AR, MR
Septal defects	AR, MR
Atrial myxoma	MS

* AR = aortic regurgitation
AS = aortic stenosis
MR = mitral regurgitation
MS = mitral stenosis

Table V
Starr-Edwards Valve Replacement.
Hospital and Late Mortality Per Cent.

AUTHOR AND REFERENCE	VALVE REPLACED AORTIC	 MITRAL	 AORTIC AND MITRAL
Effler (16)	27	18	
McGoon (18-20)	22 →0*	22 (H)‡	
Mulder (21)	29		
Nelson (22)	13	16	
Nichols (23)		25	
Starr (15, 17, 24)	30 →13†	19	19
Scannell (12)	20		30
Zerbini (11)	17	22	70

‡ (H) = Hospital mortality only, in this series.
* Zero mortality in last 100 cases, in one hospital.
† 13 per cent mortality in most recent series.

ial functional improvement expected from a prosthetic valve is obtained at the price of considerable operative mortality, and an appreciable incidence of complications[15] such as thromboembolism (17 per cent), annular leaks (26 per cent), anemia, bacterial endocarditis, persistent ventricular failure, and fatal arrhythmia. Mortality data from everal reported series are listed in Table V for eference. The great influence of the severity of the esion on mortality is indicated in Table VI. The data of Tables IV-VI, and of Figures I and II, refer o individual valves. Since rheumatic heart disease s often multivalvular and progressive, the estimates of medical and surgical prognosis for the predominant lesion must also allow for other valvular pathology which may be, or may become, an mportant source of disability when the major esion has been repaired. No data are available at he present time to allow any more than a gross mpression of the proper weighting to be given uch collateral valve lesions.

B. Selection

If valve surgery were safe and curative, there would be no hesitance in selecting patients for operation as soon as cardiac enlargement or pulmonary venous hypertension were identified, since partly irreversible changes in the myocardium and pulmonary vessels might be variably advanced by he time the patient attained a Class III status. However, mitral and aortic valve lesions are characterized by naturally long courses in the absence of symptoms (Figures I and II) or objective signs of severity, and it is unlikely that operative intervention can improve the prognosis of such mild Class I) lesions. On the other hand, in view of recent rapid technical developments in valve replacement and improvements in postoperative management, the insistence on severe (Class IV) disability before selecting a patient for valve replacement or repair is no longer justified, since this will seriously compromise his chance of surviving the operation or of regaining a lasting Class I-II status. Selection for mitral commissurotomy is warranted at an earlier stage of disability than is selection for valve replacement in view of the presently higher risk of the latter operation. It must also be kept in mind that a patient's disability depends not only on the severity of his valve lesion, but on his age and responsibilities as well.

On the basis of these considerations and the data regarding severity, prognosis and surgical mortality, some general conclusions regarding selection of a patient for mitral or aortic surgery may be stated:

1) Patients with predominant mitral stenosis should be selected for closed mitral commissurotomy when progressive symptoms begin to interfere with their ordinary way of life in spite of medical treatment and are accompanied by objective clinical and laboratory evidence of left atrial hypertension. When there are objective signs of severe mitral block, commissurotomy is warranted even though symptoms may be present only with the more strenuous forms of ordinary activity (Class II patient). If the valve is calcified, slightly regurgitant, or has "re-stenosed" after previous repair, an attempt at closed commissurotomy is warranted, but only with the understanding that the approach may have to be revised on the basis of operative findings. Therefore, under these conditions, the patient should qualify for valve replacement, in case this is found necessary at operation.

2) Class III patients with objectively severe aortic stenosis should be selected for aortic valve replacement or in rare cases for valvuloplasty without replacement, when angina, syncope or progressive dyspnea can be related to the lesion. The possibility of coronary vascular disease as a chief or major contributing cause of disability must be excluded, though its demonstration by coronary angiography does not necessarily imply an unfavorable result.[16] Congestive failure is not a contraindication to operative intervention if it responds to medical management.

3) Class III patients with mitral or aortic regurgitation should be selected for valve replacement when their symptoms are disabling for their particular way of life, or when there are objective clinical and laboratory signs of rapidly progressive anatomic or functional pathology. A more reserved approach seems warranted for those patients who need replacement of both mitral and aortic valves. Although one report indicates the same mortality for replacement of two valves as for one,[17] (Table V), it seems more reasonable to accept other reports which indicate a greater mortality from bivalvular surgery.

4) The high operative risks in Class IV patients are not necessarily prohibitive, and post-operative improvement of the functional status of such patients is sometimes dramatic. It is therefore difficult

Table VI

Operative Mortality Related to Disease Severity

	MORTALITY %		
OPERATION & (AUTHOR)	CLASS II	CLASS III	CLASS IV
Valve replacement (Zerbini, '65)	7	30	71
Mitral Commissurotomy (Ellis, '64)		3	22
	MEAN PULMONARY ARTERY PRESSURE, MMHG		
	20-40	40-60	60-80+
Valve replacement (Nelson, '64)	0	30	100

References: Zerbini (14); Ellis (2); Nelson (10).

TABLE VII

IDEAL CRITERIA FOR SELECTION FOR VALVE SURGERY (RHD)

Symptomatic functional impairment (Class III)
Objective hemodynamic disorder, mod. severe, progressive
Predominantly single valve lesion, especially mitral stenosis
Age less than 60 years
Myocardial contractility preserved
Limited pulmonary vascular disease
No right heart failure

to define the characteristics of those patients for whom operative intervention is clearly contraindicated. Almost no patient with pure and predominant mitral stenosis should be denied closed commissurotomy, even when pulmonary vascular diease has led to persistent right heart failure. On the other hand, left or right ventricular failure which persists in spite of adequate medical management in a patient requiring aortic or mitral valve replacement weighs strongly against operative intervention, though no exact line of rejection is definable.

Summaries of the characteristics of the generally "ideal" case for surgery, and of the usual criteria for rejections are attempted in Tables VII and VIII.

As surgical techniques improve, the above selection criterea will undoubtedly require further modification, particularly with respect to operative intervention earlier in the course of acquired aortic and mitral valve diseases.

The author acknowledges, with appreciation, the participation of many other physicians in the care of the patients who were the basis for this report, particularly Drs. Michael Hume and Horace C. Stansel, Jr., who performed the valve surgery, and Drs. Richard E. Fearon, Florencio A. Hipona, Richard L. Kahler, and Renato J. Rojas, who performed the diagnostic cardiac catheterizations and angiography.

TABLE VIII

CRITERIA FOR REJECTION FOR VALVE SURGERY (RHD)

Mild or absent symptoms on ordinary activity
Minimal physiologic impairment
Stationary symptoms interfering little with a way of life convenient for the patient.
Symptoms largely related to other causes
  a) non-cardiac disease
  b) myocardial failure
    coronary disease
    arrhythmias
Polyvalvular disease of balanced severity and moderate functional impairment
Advanced disease with severe R.V. or L.V. failure (line is uncertain)
High operative risk where patient can safely await further technical improvements, under close medical observation.

EXAMPLES OF CASE EVALUATION AND SELECTION

Abbreviations as for Tables I and II.
All pressures expressed in mmHg.

1) *Operative aortic stenosis*

52-year old female; Class III with exertional dyspnea, angina, mild edema responding to dig. and diuretics.

ECG—LVH. Grade 4 ejection murmur, diminished S_2.

X-ray—LVH, valve calcium, post-stenotic aortic dilatation.

Cath.—RV—33/6, LV—208/10, mean systolic aortic gradient (MSG)—76, Valve area—0.5 cm², angiography—rigid aortic valve.

Conclusion: aortic valve replacement.

2) *Operative aortic regurgitation*

39-year old male; Class III with severe exertional dyspnea, and occasional angina.

ECG—LVH and "strain." Severe murmur, Corrigan pulses.

X-ray—LV enlargement; wide pulsation of aorta.

Cath.—RV—22/3, LV—150/8-13, Aorta—150/60, LA—12 (mean), Angiography—3+ AR.

Conclusion: aortic valve replacement.

3) *Operative mitral stenosis*

28-year old female; Class III with exertional dyspnea for five years and recent ankle edema relieved by diuretics.

ECG—RVH—Grade 3 diastolic murmur, opening snap.

X-ray—Large PA and LA. No calcification.

Cath.—RV—60/30, LA—23 (mean), LV—130/3, mean diastolic gradient (MDG)—20, Valve area 0.4 cm².

Conclusion: closed mitral commissurotomy (good 10-year result).

4) *Operative mitral regurgitation*

33-year old female. Class III-IV with exertional dyspnea for seven years and CHF for 18 months with progressively less response to medical treatment.

ECG—LVH. Holosystolic apical murmur, prominent S_3.

X-ray—Enlarged LA and LV. Angio—4+MR.

Cath.—RV—55/28, LV—112/14, LA—21 (mean), 35 (V-wave).

Conclusion: mitral valve replacement.

5) *Problem case—where should line for rejection be drawn?*

51-year old male, Class IV, with long-standing RHD. Mitral commissurotomy at 47 after eight years of CHF. Return of CHF after four years in spite of full medical treatment.

ECG—non-specific, atrial fibrillation. Double murmurs at aortic and mitral valves (MR murmur predominant).

X-ray—Marked enlargement, all chambers. Calcium, both valves.

Cath.—RV—52/11, LV—180/21, LA-19 (mean), 27 (V-wave). Aorta—154/78 angiogram: MR—4+, AR—2+. MSG—26, MDG—2.

Conclusion: Aortic and mitral valve replacements. Good result (Class IV→Class II-III).

6) *Problem case—marked pulmonary vascular disease.*

47-year old female; Class III with moderate exertional dyspnea for one year. Five pregnancies without difficulty. Still active at home with only moderate fatigue.

ECG—RVH. Apical systolic and diastolic murmurs; opening snap.

X-ray—Moderate LA and RV enlargements; abnormal pulmonary vascular pattern. Angio—marked pulm. Atherosclerosis (magnification film).

Cath.—RV—93/4, LV—103/8-10, LA—27 (mean), 33 (V-wave), RA—3.

Conclusion: mitral valve replacement: died in low-output state.

7) *Problem case—moderate polyvalvular disease.*

40-year old female, Class III, with first CHF symptoms during pregnancy at 27. Moderate exertional dyspnea and occasional ankle edema on full activity, dig. and diuretics.

ECG—LVH. Double murmurs at aortic and mitral areas.

X-ray—Marked enlargement of LA and LV. Angio. AR—2+, MR—2+.

Cath.—RV—35/3, LV—130/3,LA—11 (mean), 19 (V-wave). Aorta—145/75, MDG—8.

Conclusion: defer operation (risk of 2-valve replacement not warranted).

8) *Problem case—symptoms due to other cardiac disease.*

50-year old female, Class III-IV, with progressive CHF symptoms for eight years and recent attacks of pulmonary edema associated with chest pain.

ECG—LVH, IV conduction defect, Q-waves of old posterior myocardial infarction. Apical systolic and diastolic murmurs, and soft AR murmur.

X-ray—2+ LA enlargement.

Cath.—RV—30/16, LV—163/4, Aorta 163/91, LA—3 (mean). Coronary angio—badly occluded right coronary system.

Conclusion: recurrent failure largely due to coronary vascular disease.

9) *Problem case: symptoms due to other cardiac disease.*

61-year old male, Class III, with recent return of edema and mild dyspnea associated with hypertension (180/110), three years after mitral commissurotomy for tight stenosis. Blood pressure normal at time of this operation. Taking prednisone for recurrent post-cardiotomy syndrome; recent flare-up when steroid withdrawn.

ECG—LVH, atrial fibrillation. Apical systolic and diastolic murmurs.

X-ray—Enlargement, LA—2+, LV—1+, RV=2+. Renal angio normal.

Cath.—RV—30/8, LV—180/12-15, Aorta—180/100, LA—8 (mean) MDG—4 (rest), 7 (exercise).

Conclusion: Disability due more to hypertension and (presumed) coronary vascular disease than to valvular defects.

0) *Problem case: severe disease with long survival.*

46-year old male, Class III; acute RF at 10 with murmur. Free AR for 10+ years (minimally symptomatic. Recent exertional dyspnea (6 months) responding to dig. Still fully active as a grocery store manager.

ECG—LVH. Murmur and signs of free AR.

X-ray—marked LVH. Angio —4+ AI, 2+ MR.

Cath.—RV—63/12, RA—6.6 (mean), 12 (A-wave), LV—165/32. Aorta 114/51, LA—27 (mean), 32 (V-wave).

Conclusion: Aortic replacement advised—five years ago!

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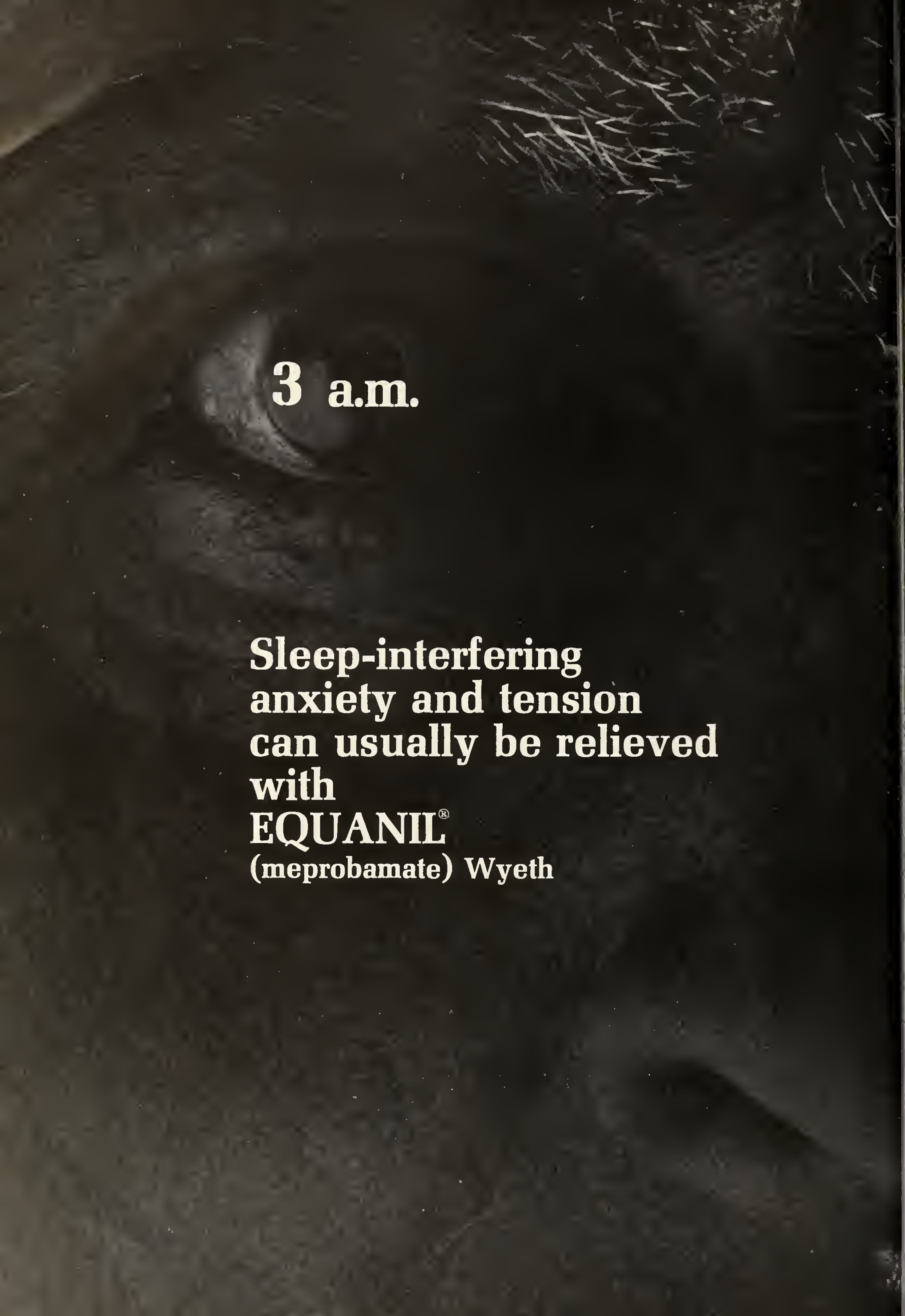

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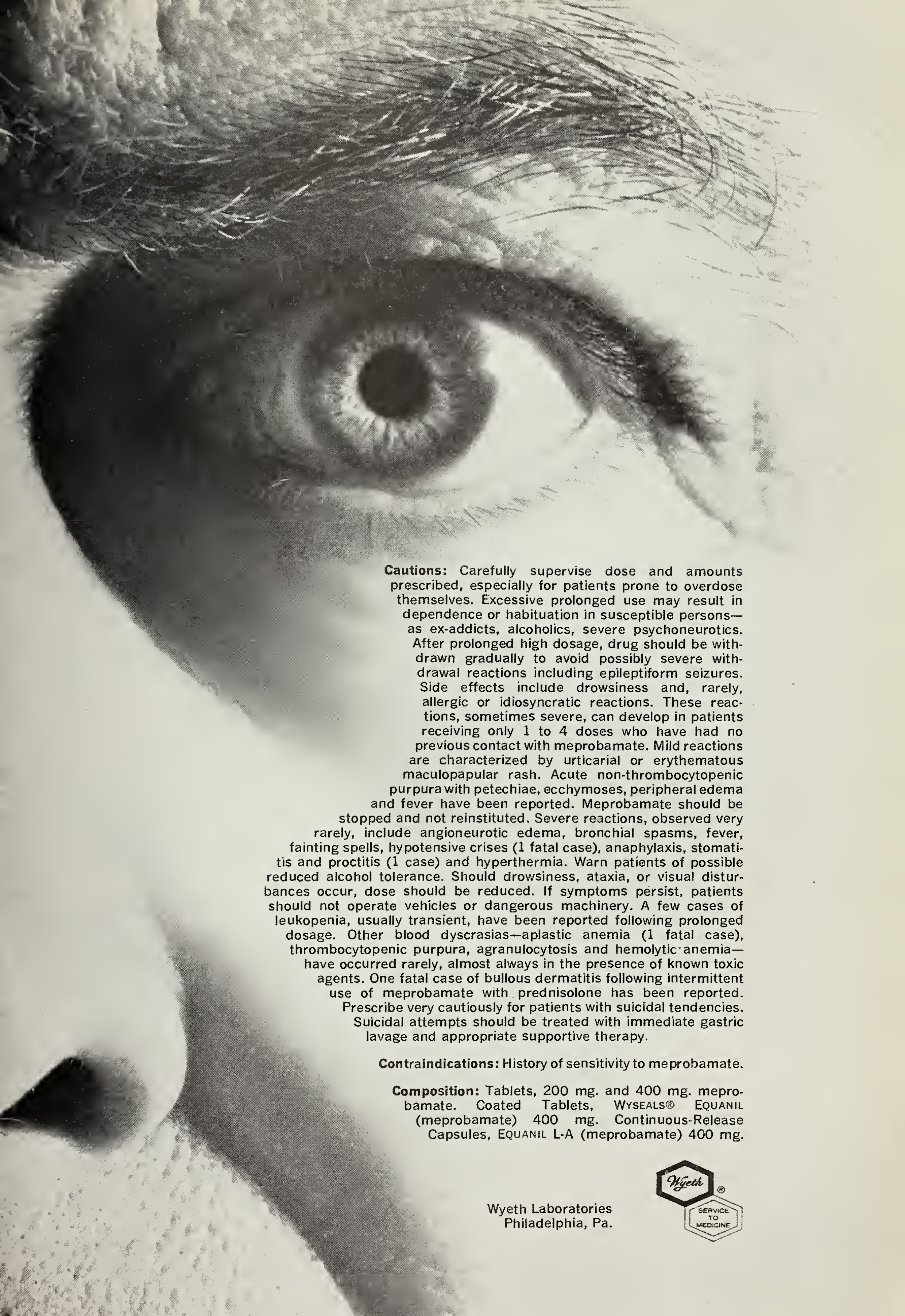

Cautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use may result in dependence or habituation in susceptible persons—as ex-addicts, alcoholics, severe psychoneurotics. After prolonged high dosage, drug should be withdrawn gradually to avoid possibly severe withdrawal reactions including epileptiform seizures. Side effects include drowsiness and, rarely, allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute non-thrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. Meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Warn patients of possible reduced alcohol tolerance. Should drowsiness, ataxia, or visual disturbances occur, dose should be reduced. If symptoms persist, patients should not operate vehicles or dangerous machinery. A few cases of leukopenia, usually transient, have been reported following prolonged dosage. Other blood dyscrasias—aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia—have occurred rarely, almost always in the presence of known toxic agents. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. Prescribe very cautiously for patients with suicidal tendencies. Suicidal attempts should be treated with immediate gastric lavage and appropriate supportive therapy.

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THE PRESIDENT'S PAGE

Hospitals Under The Fluoroscope

During the first hour (660 miles) of jet flight to the AMA Clinical Congress at Las Vegas in November, a physician from a nearby state complained to me that the hospital where he worked was inconveniently located for his patients, facilities were antiquated, admission was difficult, administrators were intolerable, the resident staff was inadequate, nurses were unavailable—in short, nothing was good. During the next several hundred miles, his complaint took a turnabout. In strong, uncomplimentary terms, he voiced resentment and complete disagreement with the attitude of a committee on accreditation which had informed him that his hospital was no longer acceptable by current standards, but he wasn't going to do anything about it. This reaction is an example of the curious desire of some to cling to the status quo, though it may be a borderline ghetto, even while federal money for improvement is readily available. Very likely it is understood by psychologists.

Despite this phenomenon, in the last decade there has been change and improvement. Now modern hospitals often have no more than 2-4 patients in a room. There may be the niceties of air-conditioning, faster elevators, privacy of lavatories, choice of menu, relaxed visiting rules, TV, and many others. Nevertheless the changes have not kept pace with new needs and demands for quality medical care that rapid advances in medical science and technology can now provide. Certainly there might be greater provision for equipment used in new electronic techniques of diagnosis and monitoring. New designs for hospitals and allied facilities are necessary to accommodate the special requirements for differing types and phases of patient care.* An endeavor should be made to make available within the hospital complex a variety of facilities tailored to accommodate the changing physical status of the patient. Surely heated bathing pools for therapy, kitchenette living, and shopping arcades for the convalescing are visionary but not entirely inconceivable for future health centers.

Of even greater urgency is the need to give proper direction to the evolving new relationships of hospitals to medical affairs in general. There is a widely expressed opinion that hospitals have responsibility not only to provide comprehensive community health care but also to be suitably oriented in the field of medical education. Since it is the trend to place a high degree of emphasis on hospital experience as essential to preparation for medical practice, this latter function should be given considerably more attention. Just as we need not only doctors and administrators but also engineers and informed architects to assure the construction of maximally functional *physical* plants, so the combined efforts of academic leaders, clinicians and, indeed, the enlightened public are required to bring this valued *educational* role of the hospital to fruition. One example of this need is apparent when we consider the large number of graduates of foreign medical schools who come to the U.S. to complete their training in our hospitals. In 1965 more than 18,000 candidates took ECFMG examinations with such potentiality. In many of our hospitals today the majority of the resident staff studied abroad. Some will return to their native countries, others will remain to practice here. To maintain our high standards of training of physicians, new techniques of post-graduate and continuing education possibly employing widespread inter-hospital exchange of personnel and combining of resources, appear to be indicated.

Orvan W. Hess, M.D.

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* LIFE—Dec. 2, 1966.

FROM THE GENERAL MANAGER'S OFFICE

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SUMMARY OF ACTIONS COUNCIL MEETING

Thursday, December 8, 1966

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Hess, Bradley, Goldberg, Brandon, H. Caplan, M. Caplan, Polivy, Rogol, Grendon, Abbot, Spitz, Hastings, Shepard, Ayres, Nolan, Ciccarelli, Cramer, Fabro, Grant, Pelz and Roch. Also present were: Mrs. Lindquist, Mr. Villano, Mr. Chilcoat (AMA) and Dr. Richards. Absent were: Drs. Gardner, Weise, Sr., W. Martin, Egan, Petrie, Wilson and Palomba.

II. Routine Business

Approval of Minutes

As printed and distributed, it was VOTED to approve the minutes of the meeting of November 17, 1966.

Life Membership

It was VOTED to approve an application for Life Membership received from the following Active Member of the Society:

Frank T. Genovese, Danbury (FCMA)

Appointment to Editorial Committee of Journal

It was VOTED to appoint Joseph L. Belsky, Ridgefield, a member of the Editorial Committee of the Journal, to replace Hugh K. Lena, New London, resigned, for the balance of the 1966-67 term.

Participant—Conference on Hospital Infections

At the request of the Planning Committee for the Conference, it was VOTED to ask Max Caplan, Meriden, to participate in the Conference as a CSMS representative chairing one of the program sessions. Dr. Caplan has been serving as a member of the Planning Committee since its formation early in 1966. The Conference on Hospital Infections will be held at Valle Steak House, Hartford, April 12-13, 1967.

III. Old, New And Special Business

Report—CSMS Committee on Relative Value Study

In a November 17 letter, addressed to Orvan W. Hess, President, the Chairman of the CSMS Committee on Relative Value Study, Stewart P. Seigle, informed the Council of current and projected activities of the Committee. In brief, the letter stated that the Committee has been "dormant" since last Spring; has not been pursuing its study of possible revisions of the unit values assigned to certain procedures (to be recommended by the various participating sections and groups); and that its Chairman feels the Committee might well be disbanded and its duties taken over by the Committee on Third Party Payments.

Following considerable discussion, it was VOTED to accept Dr. Seigle's letter (report) as information only; to urge the Chairman to keep the Committee active, at least until the next Annual Meeting of the House of Delegates; and to request the Committee to complete the work of updating the CSMS Relative Value Schedule (suggesting appropriate changes in RV units) and to report on same to the Council by mid-February.

Minutes—CSMS-Connecticut General Meeting on Medicare B

It was VOTED to receive as information copies of the minutes of the November 28 meeting between CSMS and Connecticut General liaison representatives on the Medicare B program, and to transmit this information to the House of Delegates. It was further VOTED to request the CSMS liaison representatives to draft a policy statement on "medical necessity" for Council consideration, such statement to include application of that term to the patient, as well as to the physician.

Report—Advisory Committee to Commissioners of Welfare, Finance and Control

It was VOTED to accept, as information, a report filed by the Advisory Committee on two meetings with the Commissioner of Welfare at which were discussed plans for implementing a Title XIX program of Medical Assistance in Connecticut, with special reference to the embodiment of the Society's policies on "usual and customary fees, as determined at local level" in such plans for implementation. Pursuant to extended discussion of the report, it was VOTED:

> That the Council reaffirm the Society's policies on payment of physicians on the basis of their "usual and customary fees, as determined at local level", and appoint a special committee to

determine what legislation will be necessary to introduce and/or be supported at the next General Assembly to implement a Title XIX program of Medical Assistance in Connecticut in keeping with these policies; and

That the Council appoint this special committee, to be chaired by the President of the Society, with the following composition: The State Society officers; the Chairmen of the Committees on Third Party Payments and State Legislation, and of the Advisory Committee to the State Commissioners of Welfare, Finance and Control; the Society's legislative agent and legal counsel; and the General Manager; and

That this special committee meet *forthwith,* and report its recommendations to the Council at a meeting to be called before the last week in December.

It was further VOTED to report this action to the House of Delegates.

Discontinuance of CSMS-AMA Direct Wire Service

Having learned from AMA that, after December 31, 1966, the full costs of maintaining and operating the TWX equipment installed at the headquarters building must be borne by the Society (AMA was formerly paying for rental), it was VOTED to discontinue the Society's participation in the TWX network and to request AMA to arrange to have the equipment removed from the premises at 160 St. Ronan Street, New Haven.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on December 8, 1966. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT OPPORTUNITIES

PSYCHIATRIST — full-time for small, but expanding psychiatric inpatient service in general hospital. Short-term therapy provided on open ward. Also, Mental Hygiene Clinic and Day Treatment Center on hospital grounds which offer continuity of care. There will be opportunities for teaching paramedical personnel and inservice programs. Salary dependent on qualifications. Excellent fringe benefits. Apply: Chief of Staff, VA Hospital, Newington, Connecticut 06111.

PEDIATRICIAN—Large multi-specialty group is looking for fourth man for the Department of Pediatrics in a large city in Connecticut.

SENIOR PHYSICIAN—Physician with training in internal medicine needed for ward physician in a general medical ward in fully accredited State Veterans general medical and surgical hospital. Excellent fringe benefits, including furnished house or apartment and maintenance, when available, at low cost. Salary range: $13,040–$17,040. Contact: E. O. Buetsch, Personnel Officer, Veterans Home and Hospital, Rocky Hill, Connecticut.

HOUSE PHYSICIAN—Diversified duties in 135-bed accredited voluntary hospital. Connecticut license required. Monday through Friday and every other Saturday morning. Salary: $15,000 yearly plus 3-room furnished apartment. Contact: Administrator, Park City Hospital, Bridgeport, Connecticut 06604. Telephone: Area Code 203, 368-0201.

PLACEMENT WANTED

OBS-GYN—Board eligible, 31 years old, seeks association leading to partnership. Will complete military obligations February 28, 1967. Had 4 yr. residency, fully trained.

RADIOLOGIST — Board eligible, Connecticut license. Would like to do locum tenens for months of January and February.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

IMPORTANT NOTICE

Re: Society-Sponsored Overhead Expense Plan

Group Insurers, Inc., New Haven, administrators of the Society-sponsored Overhead Expense Plan, have announced another reduction in rates—this time benefitting enrolled members under the age of 40. Effective November 1, 1966, premium charges for this group will go down appreciably. For example, under-40 members who have been paying $165 annually for $1,000 of coverage per month will now pay only $145, and comparable savings will be realized by those insured for lesser amounts. Refund checks will be forwarded shortly to subscribers who have already paid their premiums prior to the rate reduction's effective date, November 1.

In announcing the change, the Group Insurers agency states: "We expect to continue this policy of periodic rate review in the future, and to add new benefits to the Plan whenever experience permits. To our knowledge, we are offering the most comprehensive overhead expense plan available anywhere but it is our goal to constantly improve it."

SUMMARY OF PROCEEDINGS

HOUSE OF DELEGATES — SEMI-ANNUAL MEETING

Berlin, Connecticut — December 8, 1966

At the semi-annual meeting of the House of elegates, December 8, 1966, a considerable mount of business was transacted. Among the ore important items were:

The 1967 Budget

As recommended by the Council, it was voted to pprove a budget for the coming year, and to ssess membership dues at the current level of 50.00. Barring unforeseen expenses, it is expected hat a modest pay-back to reserves depleted from 960-65 may be possible.

Title XIX Program Of Medical Association

Recognizing that implementation of the new itle XIX program of Medical Assistance (author- ed by P.L. 89-97) will have substantial effects on oth the socio-economics and the quality of medi- al care in Connecticut, the House voted to initiate n active legislative program at the next General ssembly to protect the proper interests of physi- ians and patients alike. Reaffirming support of the olicy of reimbursing practitioners on the basis of heir "usual and customary fee, as determined at ocal level"; of "freedom of choice" by all con- erned with medical care; and opposition to gov- rnment control or interference with "the practice f medicine by licensed physicians and the manner n which medical services are customarily pro- ided," the Delegates directed the Council and ppropriate committees to seek to achieve these oals in the implementation of the Title XIX pro- ram.

Report Of The Council

Presented by Stevens J. Martin, Hartford, Chair- nan, the House accepted a comprehensive report n the activities of the Council since the annual neeting in April. Many of the recommendations nade in the report constituted the bases for ac- ions taken by the Delegates.

KEY RESOLUTIONS ADOPTED

Recommended by the Council, the House voted to adopt three resolutions as follows:

I. Subject: Standards Of Eligibility For Medical Assistance

Whereas: The stated purpose of the Congress of the United States, in enacting Title XIX of P.L. 89-97, was to provide for the tax-supported financing of comprehensive, high quality medical services only for those persons found by the individual states to be totally indigent and/or "medically indigent"; and

Whereas: It is the responsibility of the legislatures of the individual states to establish standards of eligibility for entitlement to benefits under such Title XIX programs of Medical Assistance; and

Whereas: In several cases, state legislatures have imprudently established standards of eligibility at levels which entitle as much as 50 per cent of the general population (specifically, New York) to such benefits, with attendant incalculable but enormous costs to all taxpayers; and

Whereas: The Congress has already recognized its error in not placing limits on the standards of eligibility for Medical Assistance which the individual states may establish; therefore be it

Resolved: That the House of Delegates of the Connecticut State Medical Society urge the 1967 General Assembly, in enacting statutes to implement a Title XIX program of Medical Assistance in Connecticut, to seek to accomplish only what is intended by the Congress, and, thereby, to establish standards of eligibility for entitlement to benefits under the program which will reflect humanitarian but fiscally prudent definitions of indigency and "medical indigency" in this State; and be it further

Resolved: That the House of Delegates direct the Council to undertake effective legislative activities toward this end at the next session of the General Assembly.

II. Subject: Statutes Implementing Title XIX (Medicaid) In Connecticut

Whereas: In Title XVIII of P.L. 89-97 (the Medicare Law), there appears a disclaimer as follows: "Section 1801: Nothing in this title shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided. . . ."; and

Whereas: The purpose of this disclaimer is to assure that the implementation of Title XVIII of P.L. 89-97 will not interfere with the licensed physician's professional judgment, his usual and customary methods of practice, his relationship with his patients, or the highest quality of medical services he is competent to provide; and

Whereas: It is the stated intent of the Congress that the recipients of medical assistance under Title XIX of P.L. 89-97 (Medicaid) shall receive health services of the same high quality which the general public currently receives; therefore be it

Resolved: That the House of Delegates of the Connecticut State Medical Society direct the Committee on State Legislation, in concert with the Society's staff and legislative counsel, to have introduced and support at the 1967 General Assembly a bill to accomplish the following purposes:

(a) To assure that no provisions of the statutes implementing the Title XIX (Medicaid) program of medical assistance in Connecticut can be construed as authorizing any State officer or employee to exercise any control over, or to interfere with, the practice of medicine by licensed physicians or the manner in which medical services are customarily provided; and

(b) To assure that no provision of such statutes, nor any directives of any State officer or employee based on such statutes, can be construed as authorizing any individual or agency, public or private, to exercise any control over, or interfere with, the practice of medicine by licensed physicians or the manner in which medical services are customarily provided.

III. Subject: Education Of Physicians For Family Practice

"Be It Resolved: That the House of Delegates of the Connecticut State Medical Society express the opinion that, in the best interests of the Connecticut public and the Connecticut medical profession, the Medical School of the University of Connecticut should include in its curriculum a program oriented toward the education of family doctors, in order to help remedy the shortage of such doctors in the State; and be it further

Resolved: That a copy of this resolution be sent to the Governor of Connecticut, the Dean of the University of Connecticut Medical School and the Chairman of its Board of Trustees."

Report Of The Officers

On behalf of all CSMS Officers, Orvan W. Hess, New Haven, President, addressed the House on a number of pertinent aspects of membership in organized medicine. The full text of Dr. Hess' report follows:

Mr. Speaker, Members and Guests of the House of Delegates:

It is a pleasure to have this opportunity to come before you. A great deal is happening in medicine. In the time allotted to me I can only speak out of context and this is hazardous. I shall, therefore, limit my remarks to a subject of current significance to you and particularly to all members of this Society.

As I have travelled about the state during the last six months and tried to lend a sensitive ear to what physicians are talking about these days, I have often heard the question raised as to just what it is that medical organizations are *doing for* their members. "I pay my dues," a doctor is likely to say, "and it isn't at all clear to me what I get in return."

This, it seems to me, is a very fair question and one deserving of a frank and honest answer, and, being President of the Connecticut State Medical Society, I would like to try to offer one.

One of the aims of your Society, as expressed in the bylaws, is "to extend medical knowledge and advance medical science" to the end that the profession can better serve the public needs. Never content with the status quo, its continuous evaluation and promotion of new educational techniques and its support of research are of inestimable value in carrying out these worthy purposes.

On another plane, the American Medical Association, which, structually, is a federation of State and County Medical Associations, is dedicated to "promoting the science and art of medicine and the betterment of public health." This entails the responsibility to make available medical care, preventive and otherwise, to all our people. More practically, though, as events have dictated since those noble words were written over a century ago, a further objective of the AMA today is "service to the professional needs of members."

But a far more urgent task has been forced upon the leadership of the AMA and the State Society by the increasing intrusion of government in the field of health care—a development threatening for decades and a reality today. How to deal with this growing challenge is a vital test of our wisdom as medical leaders, our solidarity as a profession, our courage as physicians.

This is an entirely new battle, this first step toward what many term socialized medicine. It demands new strategy. We'll have to engage—become involved—to use the idiom of the day, if we are to check this advance, contain the movement and give it proper direction. This is indeed an aspect of our work considerably removed from the higher principles of organized medicine—so more on that later while we return to the question of "what membership in medicine is doing for me."

As we view how the Society helps "to extend medical knowledge" and serve the "professional needs of members" we see a fascinating picture emerging of countless activities, countless accomplishments at the national level, at the regional level (meaning in New England), and on State and County levels by many physicians, all giving of their time, energies, and talents to try to achieve these goals for the good of the physician members and the public.

I have just returned from the AMA's 20th Clinical Convention in Las Vegas, as have your President-elect, Dr. Bradley and the Society delegates to the AMA, Dr. Caplan, Dr. Dean, and Dr. Gardner. There, were gathered many of the most outstanding medical and scientific minds in the world, sharing with us the rich lode of their accumulated clinical experiences, knowledge, acquired expertise in their special fields. In few other places, and in no other way, possibly, could any private practitioner find presented so much helpful information in so short a time.

In addition to the postgraduate programs and clinical workships we witnessed demonstrations of sophisticated new electronic equipment for data-analysis, diagnosis and therapy which may become standard office equipment in the near future. And, of course, we came away filled with ideas and suggestions and information acquired at roundtables and in private conversations with colleagues from all over the country—men who, like ourselves, are dedicated to advancing medical science.

Certainly, none of us as individuals nor even as a state-wide group could have organized and operated a clinical convention of such magnitude and importance. Only a national organization, drawing its strength from the State Societies and its individual members, could put on this impressive display of medical accomplishments. Yet, it is only a single manifestation of the AMA's credo of "promoting the science and art of medicine" and serving "the professional needs of members." And it goes on year after year.

Organized medicine, and we're still speaking about the national level, develops policies and programs which form the cornerstone of our profession, not the least of which are those dealing with medical ethics, medical education and medical service. Our entire practice of medicine and our own continuing development as competent physicians in an age of fast moving technology are tied in with these policies.

I mention this because, as we all realize, medicine, as any profession in the public sphere, must have a guiding set of operating principles, constantly updated to adjust to a changing socioeconomic climate and to new scientific discoveries. This updating is absolutely necessary if we want to assure that American medicine is the best in the world. However, you and I cannot do this alone; we need strong organizations with maximum physician understanding and member participation. By the same token, never before has the individual doctor had greater need to belong.

What is emerging here is a picture of organized medicine as the collective advocate of the physician and, indirectly, of the public. Organized medicine is in part the lookout in the crow's nest watching for dangerous trends, but it is also the beacon to help direct the medical profession past the treacherous shoals through which our progress as a profession and independence as physicians are passing.

And here is a question of my own which, I think, is fair and deserving of a frank answer. Who among us, as individuals, has the time and the inclination to serve as watchdogs for the profession, on guard against the trespasses of overzealous legislators and wild-eyed social innovators in the field of health care? Who among us, by himself, is expert enough to detect trouble spots and mount a counter attack before there is interference with the free practice of medicine?

Which of us could—or would—have taken the time from his schedule to journey alone to Washington to fight the battle against Medicare, an uphill struggle which might have ended in a stalemate save for the mood of Congress and the overwhelming votes at the command of the Administration? How many of us would have been knowledgeable enough and persistent enough in this effort as to stay with the legislation until some reasonable safeguards for the medical profession were written into the act?

The obvious answer to all these questions is, of course, very very few. No physician is sensibly asked to take on tasks of such potential consequence singlehandedly. But, we can do it,—you and I—through the medium of organized medicine, as active dues-paying members in our county associations, State Society, and American Medical Association.

Active support is imperative; and active membership participation is indispensable. Without it organized medicine would cease to exist or, at best, become weak and ineffective, a faint voice shouting into the wind.

To be an effective member of the profession no one asks that each doctor take sword in hand and charge. It is not required that everyone be an activist. To those who are anxious to serve in some area of organizational responsibility I can only say knock—the door is always open. To all others, I urge them to get behind us—we need their support and strength.

I felt I had such support when I attended the White House Conference of medical leaders on the eve of the implementation of Medicare. I was there to learn for our membership just what steps the Department of Health, Education and Welfare and the Social Security Administration were taking to make this program "go." Among other things, I picked up some hints, as did other medical leaders from around the country, of the troubles we might anticipate from departmental interpretation of the Medicare and Medicaid laws.

As I returned from my visit to the White House, and an audience with the President, I found myself aware of increasing appreciation of the foresight shown by our Council and this House of Delegates in establishing a Committee on Medicare-Medicaid Experience, several months earlier, to evaluate these problems for us and to make recommendations concerning their solution.

Dr. Bradley has also helped to foster the aims of the Society in his role as President-elect. He attended, as I did, the AMA Public Relations Institute and the State Officers' Conference in Chicago in August and submitted his impressions and observations in a thoughtful and comprehensive report to the Council. Let me add parenthetically that these reports are not presented as light reading to the Council members and then filed away. Such reports are useful and often help the Council to formulate policies which may benefit all physicians in the State.

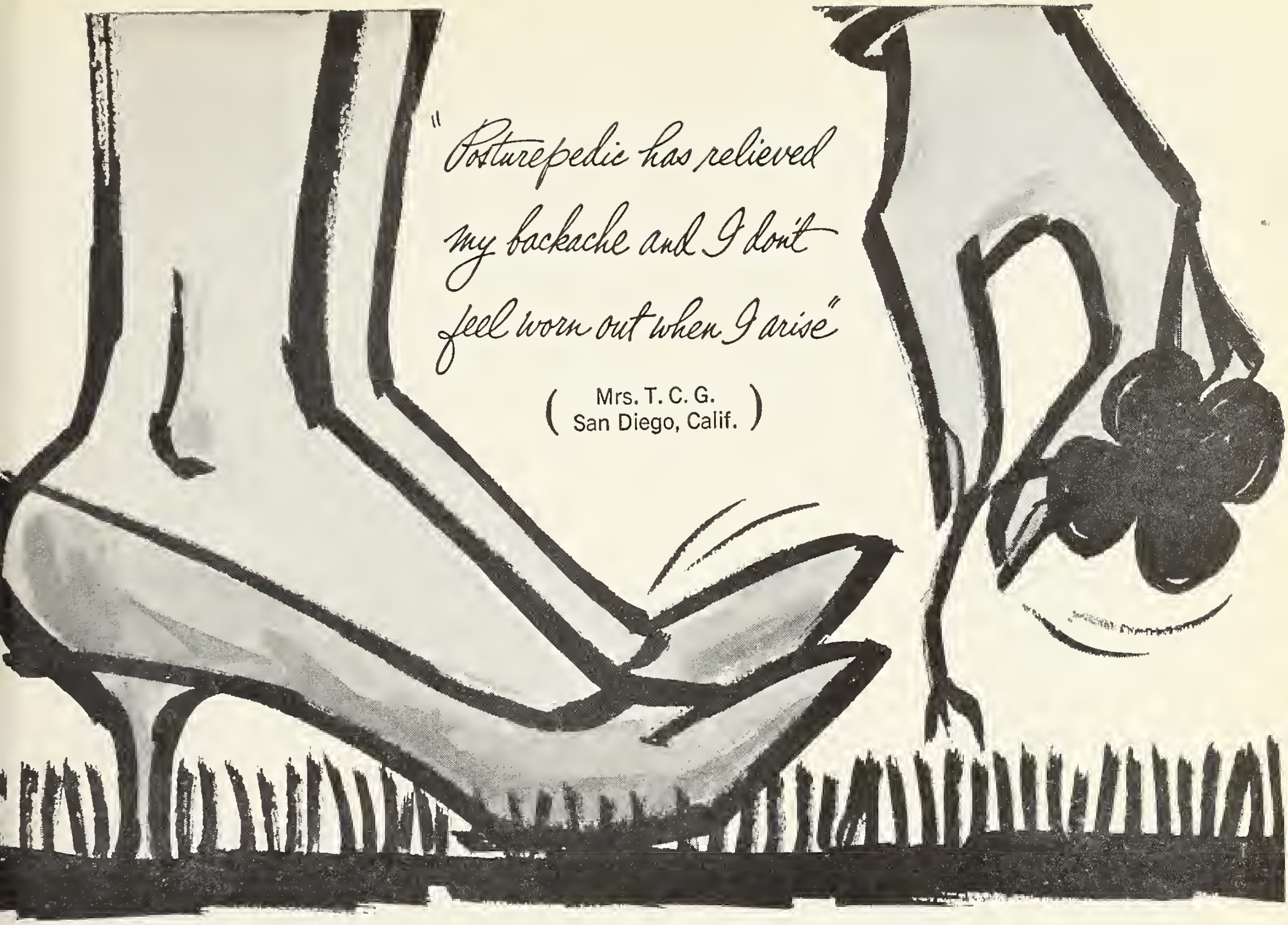
Some may look upon such traveling around by our officers, AMA Delegates and others, as so much political junketing, but I can assure you that this is not the case. The reports I have mentioned briefly—and many like them—have contributed immeasurably to the better understanding of our colleagues in Connecticut of the problems which may originate in far off places but eventually come to roost in our own bailiwick. I do not mean to dwell on the importance of meetings and reports—which demand considerable time away from practice—but I think it only proper to point out that these activities are undertaken by your elected leaders as a voluntary service to our members and in the interests of the profession.

Yet, one may still ask the question, "what do I get for my dues?" Again, I turn briefly to the AMA. With its resources it maintains 23 specialty sections, from Anesthesiology to Urology, for your continuing medical education which help you to keep up-to-date on progress in your particular field through articles published in JAMA and the association's 10 medical specialty journals.

But this is by no means the end. It's more like the beginning. Before you even learn of the existence of a new drug in your office, you can be almost sure that the AMA's Council on Drugs has given it careful scrutiny. In the war on medical quackery, the AMA cooperates closely with the Department of Health, Education and Welfare and the Food and Drug Administration. Toward the goal of high quality in medical education, the AMA works hand-in-hand with the Association of American Medical Colleges. In the halls of Congress, AMA representatives are constantly keeping a watchful eye on health legislation—evaluating it—and taking action to support what is good, oppose what is bad, and standing ready at all times to advise lay legislators on professional matters.

In these, and a hundred other areas, the American Medical Association attempts to give its members the kind of policy-based representation which we might all like to give ourselves—if only we had the time, or the knowledge, or the opportunity. This service, I submit, is not a benefit of membership which can be held in the hand or deposited in the bank—but it is a most important benefit none-the-less.

What I have just said about activities of the AMA apply, in large measure, to our activities at state level—those of the Connecticut State Medical Society. As an example: How many times have you heard a colleague say that "the Welfare Department ought to do so-and-so", or that "the General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Assembly ought to turn down such-and-such a bill"? And yet the unvarnished truth is that few physicians who seem to hold such strong opinions on these matters ever get to talk to the Welfare Commissioner personally or are disposed to put in an appearance at Hartford to make their point with our local legislators. For whatever their reasons, they often seem inclined to "let George do it", and I am happy to report that there *is* a "George" to speak and act on their behalf—in fact, quite a number of "Georges". They serve with diligence and competence on our standing and special committees —Hospitals, Third Party Payments, Public Health, Postgraduate Education, Joint Conference with the Bar and with Pharmacy, to name just a few.

And then there is the staff—the people who handle much of the routine work of the Society and assist the officers and committee members in the performance of their duties. We must all realize that the business of the Society does not stop when our meetings are over and our decisions recorded. Most of us then return to our vocation—the practice of medicine—and yet what we have said and done would be without tangible effect unless it is implemented fully through appropriate channels by the members of our staff. I pay personal tribute to all of them, and I feel that such recognition is richly deserved.

The State Society derives its strength from the component county medical associations. County members serve as Councilors, as state officers, as Delegates to the AMA, on our committees, and as official representatives to important national conferences and seminars. It is clear, therefore, that this county-state federation provides an admirable mechanism through which the collective attitudes and thoughts of all our members on a given subject—both majority and minority—can be advanced at meetings of the Society's Council, its House of Delegates, and beyond—to the AMA.

To foster this representative system, the State officers planned and conducted a Conference of County Medical Association Officers in September. The purpose of the Conference was to find out how we, as medical leaders, could do a better job. We explored, in four workshop groups, such basic subjects as the purposes and aims of medical societies in a changing age, liaison between medical societies, membership in organized medicine, and medical society policies.

In my judgment, the Conference was eminently successful. The ideas generated were at once thoughtful, imaginative, practical, and very much worthwhile. The enthusiasm of the workshop members was great. I believe that all of us felt that we had come upon a useful device to improve the effectiveness of organized medicine.

In pursuit of this desired end, we plan to schedule a second conference in the very near future for the purposes of determining ways to implement the numerous fine suggestions offered and agreed upon by the participants. I believe this demonstration of the willingness of county and state officers to seek out ways to solve problems, both old and new, is yet another intangible benefit of membership in organized medicine.

One of the cogent opinions voiced at our Conference was that the Society should continue to devote a substantial amount of its efforts to postgraduate education. All of us recognize, I am sure, that opportunities to continue our learning process are abundant in the United States — *and* in Connecticut, yet the dwindling attendance noted at most of these programs suggests strongly that there must be better ways to do this important job.

In the past several years, our Clinical Congresses have been top-drawer from the scientific standpoint but the attendance figures have been disappointing. As a consequence, the Committee on Postgraduate Education has decided not to plan a Clinical Congress for 1967, and to undertake a study of what new approaches might be used by the Society to discharge more effectively its traditional responsibility "to extend medical knowledge and advance medical science."

It is clear that there will be competition in this area of activity from many sources—particularly from government. The budget before you today may be pretty impressive to most—some $200,000—but the lavishness with which Federal funds are now being handed out makes anything under seven figures look rather anemic by comparison. Nevertheless, we should welcome competition from all sources and strive the harder to maintain a position of leadership in the educational field.

Another opinion voted at the Conference was that socio-economic matters should receive even greater attention than we have been giving them. The patterns of medical care have changed radically in the past decade or so, and will undoubtedly be subject to further alterations in the foreseeable future. The force said to have brought on these changes is the public's demand for more and better health services, and, despite the fact that private voluntary efforts have been responsible for much of the medical progress in this century which has benefitted the American people, it appears that they are answering the political call to turn more and more to government to meet their demands. However,

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social changes are inevitably accompanied by economic changes, and thus we find that government is to play an increasingly greater role in the financing—and even the distribution—of health services.

At this meeting, you will act on several reports and resolutions having to do with this swelling role of government in the socio-economics of medical practice, and I know you will give them your most careful consideration. It is rather sad, I think, that the philanthropy we have demonstrated over the years in caring for the less privileged is destined to become a thing of the past; that, in fact, we are practically prohibited by law from carrying on this worthy tradition. In its place, we are being asked to negotiate the terms of our services and to bargain as to their worth. For me, at least, this promises to be a distasteful business, and yet it must be faced up to and resolved.

As I have said before, the relatively few "Georges" of the Society must try to do the best job they can in representing all their colleagues when they are discussing these matters with the governmental officials in charge of the various programs and presenting testimony before hearings of the Congress and the General Assembly. To discharge these important duties with intelligence, with firmness, and with their eyes always on the primary consideration of what is best for the patient, these men will need every resource which we can make available to them. They are entitled to have our guidance, our moral support and our financial backing, and these entitlements will not be forthcoming unless we are assured of what I have made the central theme of these remarks—a full membership, an informed membership, and an active membership, at all levels of organized medicine.

Orvan W. Hess, *President*
New Haven

Psychotic Student In College

In campus folklore, the odd or eccentric student always turns out to be a genius, but this often isn't the way it really happens.

The lonely, disturbed young person diagnosed as a psychotic faces tough odds in college, says a report in a current publication of the American Medical Association.

Even if he receives psychiatric treatment, the ill but not completely disabled psychotic tends to leave school before graduation, and — with some notable exceptions — makes poorer-than-average grades.

A five-year study at the University of Illinois, Urbana, revealed that many of 108 psychotic students seen at the university's student health service suffered from typical characteristics of mental illness. They lacked persistence, were uncertain about goals, were dissatisfied with the curriculum, and had a "low frustration tolerance" for academic work.

This group, most of whom were diagnosed as schizophrenics ("split personalities" in popular jargon), dropped out of college three times as often as a similar group of randomly selected, non-psychotic students.

There were exceptions, however. The withdrawn schizophrenic sometimes spends much of his time studying, has little social contact, and gets excellent grades. The study found that schizophrenics' grades were widely scattered — they performed either very well or very poorly. The majority were below average, but a few received excellent grades.

The investigation also reinforced what some physicians and educators have long believed: that it requires considerable effort to maintain these students in college.

Approximately 40 per cent of the 108 psychotic students required hospitalization during their enrollment, and about half received medication.

Psychotic students represented only six per cent of the patients seen by the university's mental health division during a four-year period, yet they took up 20 to 30 per cent of the staff's time.

The investigators raised questions about how worthwhile college enrollment is for the schizophrenic. With a record of psychiatric treatment while in school, even the college graduate has difficulty getting a job, they said.

"The study indicates that some schizophrenics are capable of successful college attendance," the authors said. Any "reasonable success" of schizophrenic students justifies the effort to keep them in school, they said.

The authors are Theodore A. Kiersch, M.D. and Arthur G. Nikelly, Ph.D., both of the mental health division of the University of Illinois Health Service, Urbana. Their report appears in the July issue of the Archives of General Psychiatry, published by the AMA.

In Memoriam

Cofrances, Louis W. — New Haven; Jefferson Medical School, 1923. Dr. CoFrances had practiced medicine in the New Haven area for over 40 years. He was an Army veteran of World War I. Dr. CoFrances was on the staffs of the Hospital of St. Raphael and the Yale-New Haven Hospital. He was police surgeon for the City of New Haven in 1925. He was a member of the New Haven City Medical Society, the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. CoFrances died December 6, at the age of 67.

Root, J. Harold — Watertown; Harvard Medical School, 1918. Dr. Root practiced in Waterbury for over 40 years. He was a veteran of World War I and served with the Army Medical Corps. He was a member of the staff at Waterbury Hospital for 20 years, chief of pediatrics from 1948 to 1953, and chief of staff from 1953 to 1954. He was associated with the Waterbury Visiting Nurses for 22 years, was a former chairman of the state chapter of the American Academy of Pediatrics, past president of the Hezekiah Beardsley Pediatric Club and the Waterbury Medical Association. Dr. Root was chairman and a member of various Connecticut State Medical Society committees over the years and had served as an adviser to the state Welfare, Finance and Control commissioners. He was a member of the Waterbury Medical Association, the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Root died December 3, at the age of 73.

Doctor's Office

Ward D. Heinrich, M.D. and Reginald D. Smith, M.D., announce the opening of an office for the practice of diagnostic radiology at 24 Church Street, New Haven.

Richard Karpe, M.D., announces the relocation of his office for the practice of psychoanalysis to 236 Oxford Street, Hartford.

Witold Hawecki, M.D., announces the opening of an additional office for the practice of psychiatry at 708 Farmington Avenue, Bristol.

James P. Mooney, M.D. and James J. Doheny, M.D., announce the relocation of their office for the general practice of medicine to 299 Seymour Avenue, Derby.

Letter To The Editor

Beginning A Dialogue

To The Editor:

Dr. Fleck asks in the October issue of *Connecticut Medicine*: "Can a physician deny in good conscience patient information, instruction and devices for family planning because of his personal beliefs and values?"

I shall not presume to speak for my Catholic colleagues, but my impression is that the use of "devices" by Catholics and their prescription by Catholic physicians are morally objectionable if by device is meant a "mechanical contrivance for some purpose." (Webster's)

Dr. Fleck's specific question opens up the whole subject of the influence of religion on a physician's ethical code. He, as a psychiatrist, knows better than I about these values and influences.

The Judicial Council of the A.M.A. states: "Ethical principles are basic and fundamental. Men of good conscience inherently know what is right and wrong." I wish I could agree; I cannot. Let those who agree follow the present discussion going on in California among our medical colleagues regarding liberalization of the laws on abortion.

It seems to me that no physician should allow his own values to prevent one of his patients from getting medical advice ethically permissible to a good part of the medical profession. But he is not required to advise or prescribe contrary to his own moral code. If his ethical values, no matter how derived, conflict, he should refer the patient to someone else.

We physicians have not sufficiently discussed the ethical implications of many of the problems we are encountering: abortion, definition of life and death, treatment of the dying, artificial insemination, treatment of the biological "vegetable." These problems transcend our present codes of medical ethics; they are part and parcel of the culture of society, of religion. We physicians can, and to me should, initiate such discussion, including not only physicians, but professional ethicists, sociologists, lawyers, and the clergy.

A great problem to me is: how much pressure should a minority or majority use to impose its moral and ethical values on the whole of society? Our Constitution has put certain rights beyond the reach of the State and of a majority. It required the U. S. Supreme Court to declare Connecticut's ban on contraception an infringement on a citizen's right to privacy.

I hope Dr. Fleck's letter has begun the rational dialogue.

J. Alfred Fabro, m.d.

Torrington, Conn.

Letters to the Editor are welcome and will be published for informative and educational purposes as space permits. As with other material which is submitted for publication, all letters will be subject to the usual editing. Address all correspondence to: The Editor, Connecticut Medicine, *160 St. Ronan Street, New Haven, Connecticut, 06511.*

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Geriatric Projects For The A.M.A. Auxiliary

Programs to prepare people for their later years have been developed. In most of these the physician plays a leading role in planning and administering the program. The subjects requiring consideration have been fairly well delineated. The following areas are generally regarded as basic: (a) financing retirement-anticipatory budget planning and consideration of income supplements; (b) health—the worker's strengths and weaknesses and his family's health situation as they affect finances, housing, place of residence, activities, and family relationships; (c) activities—a substitute for the job activities the worker can afford, and replacements for former friends; (d) living arrangements—desirable or necessary changes; (e) family relationships—changes in patterns of family life in retirement and the role of children or dependents.

As an auxiliary to our husband's Medical Society, not being physicians ourselves, we are limited in our abilities—yet—limited as these are, they may still cover many spheres. A most important field in which we, the Auxiliary can be helpful is the field of education for healthful living. Good health education to be most effective in later years should be started early in life. Starting with pre-K-12th grade, we, the physician's wives should insist that our schools, public, parochial, and private, have good health cirricula with especially trained personnel to do the teaching. Thus, a child will be taught what healthful living is in every phase of life. The A.M.A. brochure "Why Health Education?", clearly delinates what is and what is not considered good health education by the A.M.A. and the N.E.A. As a nutritionist, I know that basically the nutritional requirements for the aged are essentially the same as that for the younger adult. With the recognition that the caloric requirement decreases with age, one need not, in the light of our present knowledge, alter the dietary pattern. One must be cognizant of the fact that the metabolic status of the aged is the end-result of previous experiences and that optimum nutrition should be started in the pre-natal months and maintained throughout life.

Weariness and boredom in oldsters are invited by lack of motivation reflecting a sense of values. This becomes more and more important with advancing years. They are portrayed in the habits of older persons. Therefore, establish good habits early.

As for specific suggestions, I make mention of the two projects best known to Auxiliary members, they are, "Meals on Wheels," with or without friendly visits, and "Homemaker Services."

To supplement these, Auxiliary members should organize and implement community health information meetings or forums in their communities. An excellent film for such a meeting of aging citizens is "The Critical Decades." It is a film on growing older, developed for persons in the middle years. It emphasizes the need to develop a health maintenance program in the years between 40 and 60 in order to help prevent illness or disability in later years; it shows ways in which the physician can encourage persons in this age group to seek preventive care when they are in apparent good health. It can be obtained from the Center for Mass Communication of Columbia University Press, 1125 Amsterdam Avenue, New York, N. Y. 10025.

The A.M.A. publishes a monthly fact sheet entitled, "More Life for Your Years," which Auxiliaries might endeavor to publicize more widely. In addition the A.M.A. and the State Departments of Health have films and materials on early detection of TB and other disabling illness such as diabetes, arthritis, and heart disease. Medical quackery, it's ever presence and danger must be brought to the attention of older persons. It thus becomes quite obvious that all of this requires adequate health education in the younger years as well as in adult life.

As Dr. Edward L. Bortz stated in his article on "Stress and Exhaustion," "Man's greatest battle is that of his emotional life. Old age is the *surplus* of hope over despair, of love over indifference, of motive over resignation."

Presented by Mrs. Dewey Katz, Eastern Region Chairman of the A.M.A. Woman's Auxiliary at the Twentieth Annual Conference Woman's Auxiliary to the Pennsylvania Medical Society, April 21, 1966, Harrisburg, Pennsylvania.

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1967 MEETINGS

January 17-19—New England Postgraduate Assembly will be held at the Statler-Hilton Hotel, Boston, Massachusetts.

March 30—183rd Annual Meeting of New Haven County Medical Association will be held at Waverly Inn, Cheshire, Connecticut, at 3:30 p.m.

April 12-13—Seminar on Hospital Infections in Connecticut jointly sponsored by Connecticut State Medical Society, Connecticut Hospital Association, Yale Medical School, Connecticut State Department of Health and the Communicable Disease Center of the Public Health Service at Valle's Steak House, Hartford, Connecticut.

April 25-27—175th Annual Meeting of the Connecticut State Medical Society to be held at the Hartford-Hilton Hotel, Hartford.

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Around The State

New Haven County

Board Of Governors, New Haven County Medical Association

The Board of Governors of the New Haven County Medical Association met at the Colonial House, in Hamden, on December 1, 1966 to prepare for the semi-annual meeting of the House of Delegates of the Connecticut State Medical Society, in Berlin, on December 8, 1966.

Our Councilor, Dr. Frank Abbot, reviewed the latest meeting of the Council, and our A.M.A. Delegate, Dr. Max Caplan, that of the A.M.A. House of Delegates in Las Vegas, November 28th, 29th and 30th, 1966. (Incidentally, Dr. Caplan left there by plane at 1:30 A.M. to enable him to arrive in the East in time to preside at our Board meeting on December 1st). Through the dedication of such officers we, in this County, are made aware of the current problems of the medical profession. This implementation is reflected in the participation of our members on the State level.

Another feature was the talk by Bernard R. Hammons of Hammons Associates, of Hartford, on the misunderstanding and confusion created by the changes that have taken place politically and economically in the last twenty-one years with the reduction of the glamour which once attended those in the practice of medicine. He offered plans to counteract this situation. These will be studied by our Public Relations Committee to be reported at the next meeting.

The usual social hour and dinner for the members of the Board and our guests followed. Dr. Israel S. Otis, of Meriden, a former President of the New Haven County Medical Association, recently retired from practice, was our guest of honor.

Respectfully submitted,

H. A. Levin, M.D., *Clerk*

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NEW BOOKS IN REVIEW

CONTROVERSY IN INTERNAL MEDICINE. Edited by Franz J. Ingelfinger, M.D., Arnold S. Relman, M.D. and Maxwell Finland, M.D. The W. B. Saunders Co., Philadelphia and London, 1966. 679 pp. $14.50.

Reviewed by: LOUIS H. NAHUM

— Faith must have been great since the facts are weak —

If doctors have been under the impression that treatment of many diseases are clear-cut, the data relevant and conclusive, they have another thought coming as this book on controversy clearly portrays. It points out that much of our decisions are based upon an opinion, a frame of mind that may be deprecated as tradition-bound and emotion-ridden.

This book with its 72 contributors and three editors shows as a fact that in the practice of medicine, strong opinions in many areas are held and taught in the absence of adequate data. For example in the question of treatment of peptic ulcer, it reveals that there are no more than a handful of adequately controlled objective studies in general and only one of these deals specifically with diet. In the question of using anticoagulant therapy in treatment of myocardial infarction and prophylaxis of cardiovascular disease, an important British editor is opposed whereas 90 percent of physicians in this country use it. Asymptomatic bacteriuria—should we treat it? If we do we may never know whether such treatment is necessary. We have reached such a pass that it is no longer ethically possible to observe the natural course of this and many other diseases.

If there is controversy, what should a doctor do in such instances. A book such as this serves to uncover areas where evidence is lacking whether in quantity or quality. It surely will help to force a re-evaluation of old tenets and to test the validity of shibboleths and to discourage clichés such as "it is generally acknowledged that." What is the evidence and how valid is it, is a good motto for all of us.

An analysis of some of the controversies covered in this volume reveals that they are sustained not only because of the circumscribed body of medical knowledge but also because of the frailties involved in human debate. One would suppose that a scientist differs from other people by proving what he holds to be true, However scientists are also human beings, can suffer from hazy definitions, deficiency in communication, and especially emotional attachments to a given position—to "mistruth."

It is beneficial to expose some of these weaknesses. After all, when there are differences in results or conclusions, what can be the reasons. Can opposing views be resolved and areas of agreecmnt become apparent by publicizing the controversy. A glimpse at the chapters in this book shows how difficult this really is and how badly we still are off.

Doctors are often impelled to do something when the choice is a difficult one between intervention and laisse-faire. After reading this book one realizes how absurd it is to think that unless one does something, anything, one lacks courage or jeopardizes the interest of the patient. In this wide range of topics covered with debates based on different interpretations of more or less the same material, it becomes apparent that one is not morally bound to act by a dogmatic approach in a controversial subject, especially when action itself may have its own built-in hazards.

This book is worthy of wide reading and discussion. As far as the profession is concerned, so long as the physician is willing to review, to analyze his results and agree when it is necessary to obtain more details and more accurate answers to questions that are posed, a resolution of the differences is bound to come. A healthy and objective attitude of self-appraisal must lead to a wiser and less dogma-dominated interpretation and care of our patients' difficulties.

One unexpected area not envisaged even by the editors is the medico-legal implications of this "Controversy." When the specialists disagree, what should the poor judge do?

HASHISH: ITS CHEMISTRY AND PHARMACOLOGY. Edited by G. E. W. Wolstenholme and Julie Knight. The Ciba Foundation Study Group No. 21. Little. Brown and Company, Boston, 1965. 96 pp. and 8 illustrations. $2.95.

Reviewed by: D. X. FREEDMAN

This slim volume in tiny print documents the proceedings of a study group composed of 26 scientists from various corners of the globe. Aspects of the pharmacognosy, medicinal chemistry, pharmacology, epidemiology, and of the theories and problems of drug dependence are presented and discussed. The reader must work to infer the status of a field from such symposia since succinct, scholarly and balanced judgements giving a perspective of the area rarely ensue from these tape recorded coffee-klatches. Nevertheless this is a fascinating subject. In an era when physicians must again be concerned with "drugs for kicks" as well as for tranquilization it is timely to recognize how little scientific knowledge we have of drugs which affect behavior—in spite of small cadres working with the problem. This is especially true of drugs around which a variety of habits, cults, and variably pleasureful or injurious personal and social practices can crystallize. A number of quite different drugs produce various patterns of dependence; dependence is a common factor often in the use of cigarettes, alcohol, marijuana, opium, amphetamines and LSD-25 but there are differences. Apparently these patterns differ—not only according to whether psychic or physical factors or both are operative—but on the basis of the variable purposes and consequences of persistent use. And, as Nathan Eddy notes, persistent use is not necessarily continuous use. This is familiar in the case of alcoholism in which, for example, there are persons who cannot abstain but nevertheless moderate their excess and do not suffer severe physical or social consequences; these persons are equally as "dependent as those who compulsively drink to intoxication and suffer severe physical and social psychological consequences. Such factors complicate assessments of drug abuse and especially so in the areas of hashish, possession of which is a criminal offense. There is an excellent, though scanty, presentation in this volume by J. M. Watt of the widely different social practices throughout the world and history involving the use of hashish which throws comparative light on the issue of the purported criminal consequences of the drug.

Hashish is the resin of cannabis; while past attention has focused on the flowering or fruiting tops rather than the plant itself or its seeds and leaves, pharmacological effects of extracts from any portion of the plant are now thought to be of interest. Various preparations and terms are known —hemp-seed, bangh, marijuana and in the current popular jargon, "pot". Hashish is assimilated by smoking as in a hookah (narghile) or as in reefers and is eaten or chewed and drunk especially along the North African coast. While tetrahydrocannabinol is thought to be the active component, this issue is, in fact, as yet unsolved and presents a literally sticky problem for the medicinal chemist. The pharmacologist will find a number of interesting references to relatively unknown studies and actions of the drug and, naturally (given the casual format) these are scattered helter skelter throughout the discussions. Unfortunately experts—such as Carlini in Brazil—were not present and an authoratively complete bibliography is not available. It is also strange that the testimony of another group of known experts on marijuana was not presented and sifted—i.e., that of a number of acutely observant marijuana users. Surely the problem of classifying and identifying drug effects is difficult enough without the added handicap of selecting information only from those who do not live with the drug.

The participants, nevertheless, do note various arguments on whether legal control should be exercised over marijuana; a good argument can be made (Lancet, 1963) that the drug is less harmful than alcohol. There is a lively discussion on the presumed motives for the use of hashish. Some people take drugs to gain pleasure; some to avoid pain and unpleasure; some to experience an increase in fantasy activity; others to increase efficiency or effectiveness. Whether or not the experience of euphoria is necessary for addiction or habituation is also discussed. The aim of the drug taker is to forget "what is or what will be," notes one commentator who asserts that any drug which helps a person to achieve this may (whatever the psychological experience) become a drug of abuse. Unlike meprobamate, chlordiazepoxide, barbiturates, alcohol or the opiates, withdrawal states with severe physiological and psychological symptoms are not observed with marijuana. The potential uses of the drug in depression or as a tranquilizer are explored and the abuses—the transient paranoid states, the vulnerability to disinhibition of controls (the term "assassin" is derived from hashish eater)—is also cited. This, then, is a fascinating topic, a socially important one, and from the viewpoint of psychopharmacology an interesting drug and this volume represents one of the few coordinated approaches available.

EARLY MANAGEMENT OF ACUTE TRAUMA. Edited by Alan M. Nahum. M.D. 21 contributors, 271 figures. The C. V. Mosby Co., St. Louis, Mo., 1966. 366 pp. $21.00.

Reviewed by: YALE DAVID KOSKOFF

Early management of acute trauma is a concise clearly illustrated book. It is an expansion of a symposium presented at the University of California, Los Angeles, under the auspices of its surgical department and with the support from the Accident Prevention Division of the United States Public Health Service. The Editor has been in the fore-

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front of the drive for accident prevention these last few years and has long been concerned with the importance of the critical initial phases of treatment.

With accidents becoming frequent and increasing rapidly in number, the book is extremely timely and presents contemporary views concerning the diagnosis of the acutely injured. Experts discuss trauma sustained in the various regions of the body from ankle to head. The more general aspects of the body economy are not neglected. Since the survival of such patients often depend upon prompt and accurate diagnosis and treatment, emphasis is placed upon measures necessary to resuscitate and maintain the patient. Shock, chemotherapy, radiology and cardiac arrest are given due consideration.

A unique feature of a book dealing primarily with trauma to the body is the presentation of the psychiatric management of acute trauma. The Department of Surgery of UCLA and the editor of this excellent book, Alan Nahum, who also contributes a chapter on maxillo-facial injuries, have rendered a special service to physicians who are concerned with and responsible for the earliest care of patients who have sustained acute trauma.

"*COMMUNITY MENTAL HEALTH SERVICES IN NORTHERN EUROPE.*" *By Sylvan S. Furman. U.S. Dept. of Health, Education, and Welfare Public Health Service Publication No. 1407. U.S. Government Printing Office. 1966. 215 pp.*

Reviewed by: STEPHEN FLECK

This volume is a travelogue with a wealth of detailed information about psychiatric service agencies mostly in England and a few in the Netherlands, Denmark and Sweden. It is not a comprehensive or exhaustive study or analysis of all psychiatric activities in these countries, but focuses on those which are community oriented, and supported by public funds with one exception. There is no attempt to analyse the data or distill guiding principles from the observations, let alone theory.

The most remarkable impact of these descriptions is that of the great variety of services and organizations presumably adapted to local conditions, local meaning here a city or county or region. There are "pure culture services" like Maxwell Jones' Dingleton Hospital where one type of service is given across the board, or the Studgarden School for Children in Denmark, and then there are hospitals and services that serve the widest possible spectrum of patients in different ways. By inference, but not so stated by the author, is the most impressive flexibility of British "bureaucracy," which in our routine view presents the National Health Service as an administrative monstrosity that imposes paper work and rigidities on medical care. The situation in the mental health field in England bespeaks the very opposite, namely a plethora of arrangements and authorities, including different modes of financing. Equally noteworthy is the collaboration among different professional disciplines and services, identified in turn with different mining industries in London. Local or regional independence may be almost complete in one locale and minimal in another community. One pertinent statement deserves quoting: "Netherne Hospital has become completely infiltrated with industrial work."

This in a country where unions are as jealous of their power and prerogatives as anywhere, and where reputedly governmental jurisdictions are much more ingrained than in our federal system. The facts are, however, that although on the national level industrial or vocational rehabilitation, finances, health services, and welfare services all are under different auspices, the British apparently have found ways to bring all these services together on the community level in behalf of coordinated and collaboratative patient and family care. This achievement should stir envy in American psychiatrists and community health specialists.

Unfortunately the book does not address itself to these administrative and organizational issues, and although the source of financing and nature of each authority is cited conscientiously there is no information about the evolution and development of these various arrangements. This book is, therefore, most useful in learning what is being done in these countries in the community mental health field, but not how it's being done or how it developed, which are the burning questions, and lessons to learn for American psychiatrists and other professions that are now in the beginning stages of developing comprehensive community mental health services across our land.

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CURRENT PEDIATRIC THERAPY 1966-1967. Sidney S. Gellis and Benjamin M. Kagan. W. B. Saunders Company, Philadelphia and London. 1966. 956 pp. $17.50.

Reviewed by: LOUIS H. NAHUM

The first edition of this book was a resounding success. The second one promises to be no less. The reason is that it contains 288 contributors, all expert clinical investigators and nationally recognized for their contributions to pediatric therapy. The roster of contributors, though 40 per cent different than that of the first edition, looks like the who's who in American Pediatrics.

There are 25 sections dealing with all systems, and such areas as accidents, emergencies, resuscitation, anesthesia, and some unclassified conditions such as amyloidosis and sarcoidosis, electrolyte fluid therapy, high fever, and even disorders associated with travel. The last chapter is a roster of drugs and finally an index of over 70 pages.

The authors assume that the physician has correctly diagnosed the condition for which he turns for help in therapy. But when he does, he learns exactly how the condition is being treated by a nationally recognized specialist with a more extensive experience than his own.

All medicine is changing rapidly and this is especially true in the field of therapy what with new antimicrobial agents, new vaccines, new drugs. No one physician, even the experts in this volume, are in a position to determine on his own the effectiveness and safety of all procedures. That is why there are 288 contributors and why one must perforce rely on the experience of clinical investigators to evaluate the usefulness of new therapy in a controlled setting.

A certain philosophy is explicit in this volume. It is that the vast majority of childhood illnesses require little in the way of medication and most of us can easily become guilty of overtreatment. The fewer the drugs we employ the less harm we are likely to produce, a very wholesome attitude which the reader will inherit from these experts. This does not mean that there are not numerous conditions which require the careful administration of specific drug therapy. Even though they may be infrequently encountered in practice, the physician does require a careful detailed guide in their management. This volume offers both conservatism and scientific guidance, a wonderful admixture which ensures success in pediatric therapy. It will and should be used widely not just by the family physician but by the pediatrician himself.

To the physician it will stimulate humility in the face of so many new practices. To the pediatrician it will lend encouragement in his pursuit of excellence by having at his command expertness derived from 288 wise scholars.

MEDICAL PHARMACOLOGY. Principles and Concepts. 3rd Edition. Andres Goth. M.D. The C. V. Mosby Company, St. Louis, Missouri. 1966. 668 pp. 66 figures, 23 tables. $12.50.

Reviewed by: LOUIS H. NAHUM

The author intends this book as a text for physicians and students covering the principles and concepts of modern medical pharmacology. It is of modest size having much selectivity and conciseness. It includes adequate references to the experimental literature and to review articles most of which are no later than 1963. It does have the underlying ideas, their development and importance in medical thinking. However, in some instances the medical ideas are somewhat blurred as for example in the discussion of digitalis action in which the action upon the nervous system is not emphasized as it needs to be for the practicing clinician.

Otherwise good data is available on drug effects on man which do receive especial emphasis. The book also favors areas that are expanding and that form the basis of modern clinical medicine. It places emphasis on the mode of actions of drugs in terms of interactions with their physiological and biochemical mechanisms. Doubtless in the next edition there will be considered the principle of enzyme induction which as only one example operates to interfere with the anticoagulant effects of the barbiturates.

The book is beautifully printed with blue captions which are a delight to a reader. It will be much used by students and physicians as the author aspires for it to be.

CURRENT DIAGNOSIS. A Biennial Volume of Clinical Diagnostic Methods and Evaluations. Edited by Howard F. Conn., M.D., Robert J. Clohecy, M.D. and Rex B. Conn, Jr., M.D. W. B. Saunders Company, Philadelphia and London. 1966. 843 pp. Illustrated. $19.00.

Reviewed by: LOUIS H. NAHUM

The logical foundations of making a clinical diagnosis is difficult to realize at best. There is involved memory, intuition, a practical approach to probability, perhaps and element of chance, and of course, logic. Basically one engages in the method of multiple working hypotheses, considering alternate possibilities, then eliminating one after another until the correct diagnosis finally emerges.

As knowledge advances rapidly medical science is undergoing continual and rapid change. What may have been a diagnostic entity a decade ago may be a precisely defined disorder today, but it also may represent an entire spectrum of a group of diseases today. And so we are continually in need of sorting out new disease entities as they are discovered and we need to be able to utilize new procedures and new tests.

This book is so well done that a physician who has a major symptom in a patient or who suspects a new disease can go to the index with one or more presenting symptoms and signs and find the part of the book which offers precise instructions in each step needed to confirm his clinical impression. In this way an old diagnostic method together with any recently described one will be combined to arrive at the correct diagnosis. The reader will be assisted by the expert knowledge and experience of 285 contributors of national fame. They offer a concise definition of the disease entity and discuss the present signs and symptoms, physical findings, complications, laboratory tests, and other procedures helpful in identifying the disease.

Differential diagnosis per se and a large list of alternative possibilities are not in the text, but an extensive index lists all symptoms, signs and findings in the book, directs the reader to the parts of the book where these may be found. By glancing down the index one does have a very good overview of differential diagnosis. In addition the first two pages gives all laboratory tests and normal values of clinical importance.

Of course once a diagnosis is made the next step is correct therapy. For this one will need another book.

Asbestos In Urban Air

Asbestos in the air might some day be a new hazard to urban living.

The concentration of asbestos particles in urban air probably isn't of major concern now, emphasize two medical investigators in a current publication of the American Medical Association.

They point out, however, that the wear of automobile clutch and brake linings, the weathering of asbestos roofing—even the wearing of floor tile containing asbestos—are certain to increase airborne concentrations of the material.

Inhaled in sufficient quantities, asbestos can cause lung disease, including malignant tumors.

Asbestos is virtually indestructible. The most commonly used type has a tendency to break into hair-like fibers, some of which are so small they cannot be seen with an ordinary microscope.

If inhaled into the lungs, the sharp fibers move downward, concentrating in the base of the lungs or in adjacent tissues. Protein and iron encrustations form around the fibers, producing "asbestos bodies." Man and guinea pigs seem to be the only animals in which these formations occur, but the result in their bodies can be development of a tumor.

The authors of the report are J. G. Thomson, M.D., of the Medical School, University of Cape Town, South Africa, and Wallace M. Graves, Jr., M.D., formerly of the University of Miami School of Medicine, Miami, Fla., and now of Professional Medical Laboratories, Fort Myers, Fla.

When they reviewed the autopsies of 500 Miami residents aged 15 and over, they found that asbestos bodies were present in the lungs of 30 per cent of the males and 20 per cent of the females. These findings were similar to an earlier Cape Town, South Africa, survey by Dr. Thomson.

The authors emphasized, however, that none of the deaths were due to asbestos inhalation or, in fact, to any kind of lung disease. Only a few of the males (about 1 in 17) had what might be considered significant concentrations of asbestos bodies in their lungs.

The survey did not indicate the concentration of asbestos particles in Miami air. It showed only that urban dwellers are exposed to some asbestos inhalation, a phenomenon of modern times.

"The use of asbestos has increased in amount and variety in the past 30 years to a degree unprecendented in any other common mineral," the authors said. "Few are aware of the extent to which there has been created in recent years in towns and cities what could be called an asbestos environment."

World asbestos production now exceeds 3 million tons a year, five times that of 20 years ago. The United States consumes one-fourth of all production.

In earlier times, workers in asbestos mines and factores were frequent victims of lung cancer. Factory dust control eliminated many of these hazards, but now smaller quantities of airborne asbestos are found in many places.

Commenting on the report, an editorial in the current Journal of the American Medical Association said: "Asbestos is now a hazard in an increasing variety of occupations involving asbestos or asbestos-containing products, such as asbestos cement, insulation, paint and plastic, ship building, and in the construction industry."

The lung disease observed in these workers is usually milder than that seen earlier in asbestos-factory workers. However, after being exposed to asbestos for several years, malignant tumors may develop.

"Unlike the older population which had no exposure to asbestos until recently, the young urban dweller has the exposure of a lifetime before him," the editorial said. "The investigators predict that urban air contamination by asbestos will continue to increase. What is not known is just how much asbestos must be present before (malignant tumors) result."

The report appears in the current *Archives of Pathology* published by the AMA.

College Freshmen And Smoking

When 3,567 freshmen at the University of Illinois, Urbana, were questioned about their smoking habits, the investigators found these things:

—There was an inverse association between grade average and smoking: of students with an "A" average, only 16.7 per cent smoked, while 59.1 per cent of "E" average (the lowest grade) students smoked.

—Sixty per cent of the freshmen did not smoke, and 43 per cent of those who smoked wanted to stop.

—The amount of allowance seemed to have a relationship to smoking. When parents provided full financial support, the number of freshmen who smoked was above average. The average weekly spending money was slightly over $8. When it was more than $5, the percentage of smokers was above average. Only 20 per cent of those who received sole financial support from a scholarship smoked.

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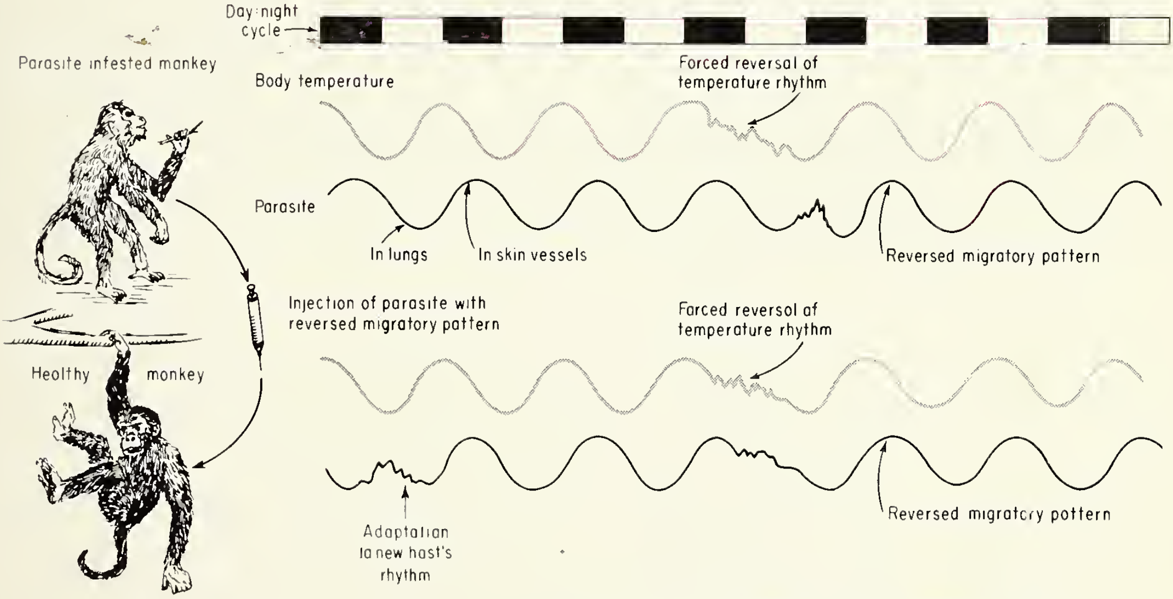
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Connecticut Medicine

editorials

Myocarditis Today

There is of course no reason why the myocardial cell should not specifically respond to an injury, no less than any other cell in the body responds to an inflammation. Fiedler in 1899 did describe primary myocarditis and then Aschoff described the specific myocardial lesion in rheumatic fever.[1] The differentiation of vascular from inflammatory disease of the myocardium became distinct after Herrick in 1912 described the features of myocardial infarction. This led clinicians away from thinking about myocarditis and towards a concept of chronic degenerative changes from vascular disease of the coronary and hypertensive type. The clinically predominant features were myocardial weakness and failure and this was poorly understood and misidentified as chronic myocardial weakness and failure sometimes termed "chronic myocarditis" or non-valvular heart disease. It was a clinical not a pathological diagnosis.

By 1940 the clinical diagnosis of myocarditis, acute as well as chronic was seldom being made except as an occasional complication of diphtheria and as a part of rheumatic fever. Non-vascular myocardial disease did come to be recognized in the form of new concepts of disease mechanisms: idiopathic myocardial hypertrophy, "idiopathic cardiomegaly". Cardiac hypertrophy of unknown cause first observed in infants but later also in adults, endomyocardial fibrosis, fibroelastosis, endocardial sclerosis, intestitial fibrosis, all derived from careful anatomical studies. Ideas about the etiology of these anatomical entities included pre-existent fetal myocarditis, defects in the development of the endomyocardium, biochemical abnormalities of the myocardium such as glycogen-storage disease, hereditary diseases, and later dietary deficiences to explain the adult form.

Recent observations of the association of a remarkably high incidence of positive skin reactions to mumps antigen in infants with the clinical features of endocardial sclerosis is highly suggestive of a relationship to mumps infection in the mother and to the concept of fetal myocarditis as the basic cause of chronic endomyocardial disease in infants and children.

The first recognition of a clinical hypersensitivity or auto-immune myocarditis was Loeffler's description of fibroplastic myocarditis in 1936. Since then in rapid succession eosinophilic granulomatous myocarditis, myocardial and vascular lesions of lupus, systemic sclerosis, polyarteritis, rheumatoid disease and granulomatous sarcoid lesions of the myocardium were described and fall into another category of myocardial disease.

With the revival of interest in the 40's in myocarditis by the pathologist the meaning of myocarditis in both pathogenesis and etiology became broader and soon included reactions of the myocardium to various types of injury as for example alcohol,[2] fat solvents,[3] rather than limitation only to bacterial infections.

During the war many autopsies were performed and out of these and extensive clinical tests there emerged the fact that myocarditis was a frequent complication of many diseases and systemic disorders. A wide diversity of diseases in which myocarditis and myocardial changes could occur sharpened the clinician's effort to make a clinical diag-

THE COVER

A remarkable example of species adaptation to twenty-four hour rhythms is found in the association between the parasitic infestation Wucheria bancrofti and its animal host. This affliction of man has been studied experimentally in monkey in order to determine what factor in man is responsible for timing the nightly migration of microfilariae—thread-like nematode worms—from the host's pulmonary vessels to the skin vessels. Since the microfilariae are ingested, and mature in, the mosquito—who transmits them to another host—their diurnal migratory pattern is an adaptive property which links the host, parasite and mosquito in a biological "vector". By reversing the normal day: night rhythms of infested monkeys it was shown that the parasite somehow uses the circadian variation of the host's body temperature as a clock for regulating its diurnal migrations. The temperature rhythm itself is a circadian clock.

nosis during life. During this period suspicion of viral etiology of myocarditis became a reality as cultural techniques for growing viruses were developed. Influenza virus A was successfully isolated from fetal cases of myocarditis in 1945 and shortly thereafter successful recoveries of Coxsackie B virus were made from myocarditis in infants and adults.[1]

Inevitably we began to think not just of acute myocarditis but of the possibility of subacute and even chronic forms of myocardial disease resulting from mechanisms of autoimmunity or hypersensitivity after the period of viremia and clinical infection had passed. It must be said, however, that today the clinical diagnosis of viral myocarditis that is made is purely presumptive, occasionally it is highly circumstantial and only rarely is it well established by isolation of a specific virus by appropriate immunological studies.

The spectrophotometric method for determining electrolytes quickly led to confirmation of the physiological role that certain electrolytes, especially sodium, potassium, calcium and magnesium, play a vital part in normal myocardial function. It became clear that quantitative alterations in the intracellular and extracellular contents of these electrolytes caused serious disorders of myocardial function. Thus was light thrown on the pathogenesis and etiology of myocardial disturbances manifested by arrhythmias and conduction disorders of hyper and hypokalemia. Selye's ideas of multiple etiologies of myocardiopathies through interplay of electrolytes and hormones perhaps will lead to understanding of myocardial abnormalities encountered in disorders of the endocrine system.

The introduction of right and left sided catheterization and selective angiography has made possible the study of altered hemodynamics in hypertrophy, dilatation, restrictive myocardial fibrosis and myocardial failure. One can now make a differential diagnosis between pericardial disease, chronic valvular disease and congenital heart disease. Recognition ol hypertrophic muscular obstruction is a direct result of application of these techniques to the old problem of subaortic stenosis which though recognized for years was not understood either in its pathogenesis or its etiology.

We now have a better understanding of factors causing cardiac dilatation and of acute and chronic myocardial development of adaptive hypertrophy of the myocardium when recovery occurs in the dilated heart. The dilated heart with a large residual diastolic volume is "overloaded" and is at a considerable disadvantage because by contracting on a larger sphere it must generate excess tension to perform the same work as a normal heart does. Thus grew the idea that we need to reduce the size of the heart and its work by reducing blood volume through salt restriction and diuretics, by use of digitalis and by prolonged bed rest to achieve compensation. It is interesting to reflect that this same idea was long ago applied in the early 19th century to rheumatic carditis and other ill-defined carditides.

With such new techniques as histochemistry, immunochemistry, physical chemistry, electron microscopy and isotope labelling, turning up new information that goes down to changes in membrane function and organelle, investigators are beginning to think of "molecular disease" in which important cellular proteins are either lacking altogether (genetic) or seriously impaired or lost by acquired disease. Heart failure may be a result of alterations in the contracting protein or defects in energy formation or in transport of electrolytes through membranes and their influence on muscle contractility especially the calcium ion. Future diagnosis of myocardial disease and differentiation from vascular inflammatory and other types of myocardial injury may be improved by using serum enzyme chemistry and determining enzymes liberated in the blood and tissues (SCPK).[4]

With all this newer methodology we can recognize myocardial disease at an earlier period and this offers an opportunity to investigate etiology and pathogenesis for prevention and treatment. In view of all this when should we employ the term myocarditis? Should we limit it to an inflammatory process in the myocardium producing an exudative or proliferative cellular reaction. If we do, what shall we call the end result of this process which is quite variable leading to cellular response and clinical features depending upon complete or incomplete restitution. Obviously the clinical sequelae must vary in each instance?

If we accept a broad view of myocarditis then it will subsume acute arrhythmic deaths, clinical features of acute dilatation and myocardial failure, syndromes of chronic recurring failure and features of idiopathic cardiomegaly. During various eras of the past there have been first splintering, then lumping of the myocarditides. We may expect that as our knowledge about the basic structure and function of the myocardium increases, so must our ideas change with it.

L.H.N.

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Nutrition And Disease

We all use special diets as an adjunct to therapy, for we know that diet does have an influence on the response of the sick. We attempt to correct nutritional deficiencies in underweight and overweight. We use special diets in various gastrointestinal disorders, kidney disease, liver and gallbladder abnormalities. We manipulate the diet to produce an alkaline or acid urine, to restrict purines. In the diagnosis and management of food allergies an appropriate diet is essential. What is important to bear in mind is that there is a close relationship between nutrition and disease. In fact, nutrition can have an important bearing on the outcome of certain infections, on cancer and drug toxicity.[1]

There is present in wheat and other foods a factor promoting the resistance of the animal to infection with Salmonella typhimurium and designated Salmonellosis Resistance Factor (SRF).[2] But the problem is very complex because involved is fat, protein content, levels of vitamin A. O'Dell found substances present in cabbage, and soybean protein that have a favorable influence on the course of Salmonella typhimurium in the guinea pig.[1] The substance itself is not an antibiotic.

There is also varying susceptibility of parasites to the action of drugs in animals depending upon the diet the animals are taking. Stibophen killed many more of the parasites, Schistosoma mansori in infected mice, if they were given a casein diet, rather than a stock diet. Similarly sulphadiazine is much more effective against a chick infection with Plasmodium gallenaceum if they were on a purified diet than if they were on a commercial stock diet.[1] It was the soybean in the meal stock which was implicated as responsible for the effect.

Nutrition has been implicated in carcinogenesis as well as in the treatment of cancer. Dietary protein can modify carcinogenesis. Tannenbaum and Silverstone [3] found a strikingly low incidence of hepatomas in mice if they were fed a diet containing 18-45 per cent casein. The same decreased tumor incidence was true in rats given a carcinogen, if they were on a high level of protein in the diet. This was not true in the case of spontaneous mammary cancer in mice and sarcoma induced by carcinogenic hydrocarbons. Obviously there is a great deal to learn about this subject before it become relevant in the human situation, although absorbing benzpyrene produced in smoked foods in Iceland is known to greatly increase the incidence of gastric cancer.

The relation of nutrition to toxicity has been known for almost half a century when Voegtlin found protection against TNT poisoning in dogs if they were on a white bread, milk, and medium fat beef diet, but no protection if they consumed a diet of bread and milk. A deficiency of protein also was found to predispose to damage to the liver by TNT. Also known is that drinking alcoholic beverages after exposure to TNT or nitrobenzene precipitates toxic symptoms. This effect on man also occurs in mice.

It was Wilson and De Eds [4] who showed that acute toxicity of thiourea could vary almost 16 fold according to the diet on which animals were maintained at the time of testing. Likewise they noted that the toxicity of polyethylene glycols on the skin of rabbits could be mitigated by feeding them commercial chow, and aggravated by feeding the animals rolled barley.

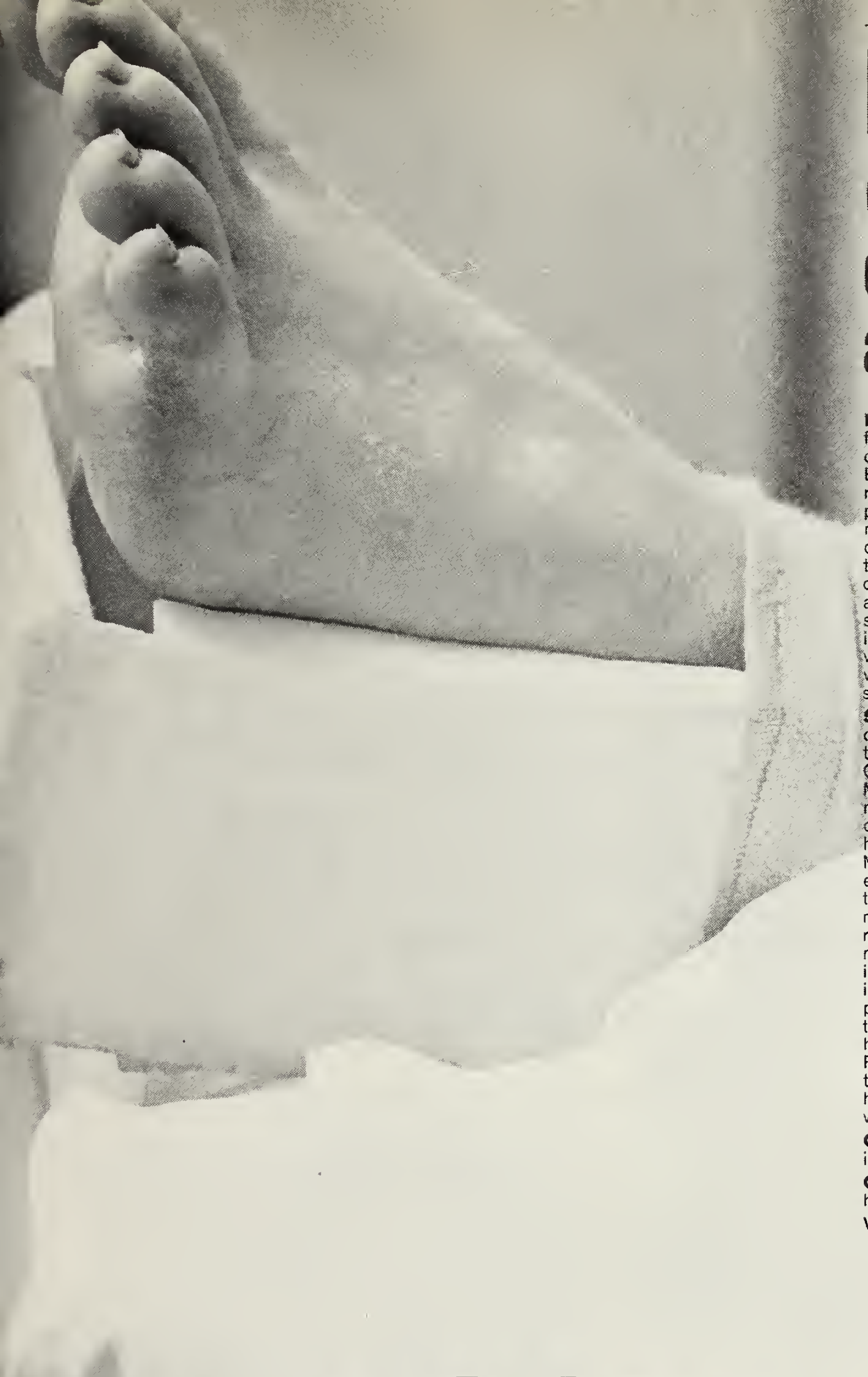
Protein an aminoacids are protective against acute toxicity of halogenated hydrocarbons, benzene, emetin, ergot, alloxan and phenol. If fat is then added to the diet it increased the toxicity of benzene, alloxan, DDT, but decreased the toxicity of cyanide.[5,6] This action of fat is not due to its aiding absorption because it also occurs when poisons in the form of vapors are presented and in the case of alloxan when it is administered intravenously. There are many other known instances in which diet plays a significant role in either accelerating or preventing the degree of action of a toxic substance.

These variations in the effect of diet on toxicity raise many questions that have received little attention. We do not know what substances are responsible for the differences in response observed with the different diets. This knowledge may be quite valuable for any individual substance. For this reason much more data must be accumulated so that we will be able to understand the relation of nutrition to biological response.

A certain kind of diet has been found by Spector and Calloway [7] to reduce significantly mortality of animals exposed to lethal doses of whole body radiation. The protective factor seemed to be in cabbage and brocoli since without it both guinea pigs and rats showed a very high mortality.

Others have also pointed out that toxic manifestations of many substances are dependent on the composition of the diet.[8] Toxic effects are very striking in animals that are kept on a purified diet and minimal or altogether absent when fed on a commercial stock ration. On purified diets an antioxidant produced significant growth inhibition, unhealthy appearance and increased mortality, signs not to be found in animals fed a stock ration. What the protective factor is has not been settled though sucrose in the purified diet has been implicated.

A high protein diet protects rats against dieldrin. Starvation protects mice against bee venom. A rat deficient in vitamin B_{12} cannot tolerate triglyceride of propionic acid. Unless chicks are fed raw kidney



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Precautions: Keep out of reach of children. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate may result in dependence or habituation in susceptible persons—as ex-addicts, alcoholics, severe psychoneurotics. Withdraw gradually after prolonged high dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance. If drowsiness, ataxia or visual disturbances occur, reduce dose. If symptoms persist, caution patients against operating machinery or driving. Give cautiously to patients with suicidal tendencies. Treat attempted suicide with immediate gastric lavage and appropriate supportive therapy

Side Effects: Ethoheptazine and aspirin may occasionally cause nausea, vomiting, epigastric distress, and rarely dizziness and CNS depression. Overdosage may result in salicylate intoxication. Meprobamate rarely causes allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. Meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioedema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. A few cases of leukopenia, usually transient, have been reported following prolonged dosage. Rarely, cases of aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported; almost always, in the presence of known toxic agents.

Contraindications: History of sensitivity or severe intolerance to aspirin or meprobamate.

Composition: 150 mg. meprobamate, 75 mg. ethoheptazine citrate and 250 mg. aspirin per tablet.

Wyeth Laboratories Philadelphia, Pa.

Weighing on his mind, too

When pain evokes anxiety and tension, thereby heightening patient discomfort, a simple analgesic may only touch on part of the problem.

This single-prescription, nonnarcotic product, however, usually provides effective analgesia *and* helps put the patient's mind at ease.

beans, vitamin E prevents muscular dystrophy. Then there is the report by West[9] which shows that aspirin when incorporated in a diet high in carbohydrate was substantially more toxic to fetal rats than when it was given in a diet high in protein. No mention in this report is the possible role of aspirin in congenital malformations. All this work clearly indicates the importance of the diet as a factor to be considered when evaluating the toxicity of a drug.

We can see that an important but a relatively neglected aspect of nutrition research is developing that should clarify the relationships of nutrition to biological response. We must remember that we need to understand not only how inadequate diets influence the way in which an organism responds to variations in his environment, but we must also learn how apparently adequate diets of differing composition also influence the organisms response to variations in his environment.

L.H.N.

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Transplantation Biology: IV. Other Considerations

Billingham[1] has estimated that in the United States renal transplantation might be able to save 60 thousand to 90 thousand lives per year. With bone, bone marrow, cartilage, skin, and liver the figure would be very much higher. Now that the effective means of overcoming the homograft barrier are practically within our reach we are becoming painfully aware of other formidable obstacles, for there are few organs that a healthy living person can donate. However, we can live perfectly normal lives on one kidney, and once it becomes possible to ensure the long term success of renal homografts it may be possible to find enough donors.

What about other organs such as hearts, livers, or lungs. It is true one can live on one lung. However, to donate a healthy lung would probably involve too serious a surgical risk to be acceptable. The only conceivable source of supply of these organs then is the cadaver. Here the problem becomes extremely complex. Few people die under circumstances in which donation of an organ is a practical possibility. With some notable exceptions, including skin, cornea and possibly limbs and lung, internal organs, certainly kidneys and livers, deteriorate very rapidly after death. In fact, the process may even have begun in the terminal stages of life.

In order to retard the process, steps must be taken immediately after death to cool the potential organ graft almost to the freezing point as rapidly as possible. An alternative is to keep the body alive with the aid of some kind of a heart-lung machine. Then there are the serious ethical and medicolegal problems associated with the employment of living or cadaver organs, for at times a prompt distinction may have to be made as to when a person is dead and how quick the organ in demand may be procured.

Even when a healthy viable organ has been obtained, it must be transplanted immediately for otherwise there arises the problem of its preservation. We know that a wide range of cells and tissues can be chilled slowly if impregnated with certain protective agents such as dilute solutions of glycerol and dimethylsulphoxide. They can then be frozen to very low temperatures (preferably to that of liquid nitrogen—196°C) and stored to what amounts to a state of suspended animation for long periods.[1] Subsequent rapid warming will revitalize them. When it comes to the preservation of organs, particularly kidneys, these methods have been unsuccessful. There is still a tremendous gap between our knowledge of the conditions required for an organ as large and complex as the kidney.

At a few degrees above freezing the useful storage life of a whole kidney is well below 24 hours. If we knew how to extend this period for only a few days it would have a considerable impact on the logistics of organ transplantation. Hyperbaric oxygen has been tried as well as attempts to inhibit metabolic activity by means of a non-toxic chemical agent. But no solution is yet in sight. A hibernating animal such as the woodchuck is able to "store" itself for many days at temperatures near freezing. Perhaps if we knew how he accomplishes this feat we might have a clue that could be fruitful in this regard.

Because of non-availability of live human donors for human renal tranplantation, a few intrepid surgeons have tried to use heterografts from baboons and chimpanzees. We were all surprised to hear that one patient was sustained for nine months with a champanzee kidney.[2] In the light of the promptness with which heterografts are usually destroyed, this result must be considered impressive. As far as man is concerned chimpanzees do not breed rapidly, are not abundant and the problem of overcoming immunity to heterografts from our near relatives the primates is much more exacting than overcoming resistance to homografts.

There are of course other therapeutic applications of transplantation in which neither problems of procurement and storage are vital. For example, there is sound experimental basis for the belief that solution of the donor selection problem will make it possible to employ "grafts" of bone marrow to correct acute destruction by drugs or radiation. Indeed there are already cases on record [3] in which hemopoietic tissue grafts from identical twin donors have been successful in the treatment of severe hypoplastic anemia.

Technically marrow transplantation is a relatively simple procedure. This rather pulpy tissue can easily be aspirated from the marrow cavity of the donor (it's loss is soon made good) and injected intravenously into the patient. The cells can find their own way to appropriate sites. At times the sites may have to be "cleared" beforehand by x-irradiation or other means, though this may not often be necessary.

Another possibility is the correction of certain hereditary or acquired deficiencies on the part of the immunological defense machinery such as hypogammaglobulinemia [4] by means of infusion of lymphocytic cells fractionated from the blood stream of well-matched donors.

Once histocompatibility tests can help us overcome the immunological hazards why couldn't it become possible to sustain the life of an individual during an acute self-limiting illness such as potentially reversible failure of the liver by temporarily uniting his circulation with that of a healthy subject. In fact, some partially successful attempts to treat patients suffering from acute liver disease by perfusing their blood through fresh isolated pig livers for a few hours have been reported.[5]

However, even when there is complete histocompatibility as in the case of renal grafts from identical twins, many kidneys succumb to the disease that destroyed the native organ. In such cases organ replacement represents treatment of a symptom rather than the basic disease process, and indicates ultimate failure for reasons not yet taken into account, such as for example absence of a lymphatic return.

And so attention is turning to the development of mechanical prostheses for organs in the same way as synthetic fibers are employed for vascular grafts. So far as other organs are concerned besides kidneys and heart, there seem to be no reasonable grounds for the belief that mechanical substitutes will be developed in the foreseeable future and the cadaver must be regarded as the only source of supply.

Billingham points out how ironic it is that the one tissue that can most easily be obtained from cadavers and which can be easily preserved at low temperatures for prolonged periods—skin—is the one against which the homograft barrier seems to be so unrelenting—much more so than for example the kidney.

L.H.N.

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Recognizing Conversion Reactions In Medical Practice

Conversion reactions are emotional conflicts which are "converted" into disturbances of the voluntary neuromuscular or sensory perceptive systems by unconscious mechanisms to produce symptoms which mimic organic disease. The question is how we as physicians can distinguish conversion reactions from organic illnesses. It is a thorny problem for many physicians. The differentiation requires first that organic pathology be demonstrated to be absent. Then the presence of certain forms of psychopathology must be recognized as present. Both of these approaches may prove to be very difficult.

The physician naturally seeks first an organic basis for eymptoms while the psychiatrist, a functional cause. Even if an organic cause is present it

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does not rule out a conversion reaction. Furthermore if a conversion reaction is diagnosed by the psychiatrist, this does not rule out the possibility of an organic illness either co-existing or causative. It is for this reason that it is necessary to evaluate the psychiatric criteria, so that both physician and psychiatrist may be in possession of a reliable predictive index to differentiate a conversion reaction from organic pathology.

Raskin Talbot and Meyerson[1] tested eight criteria in 50 patients for their usefulness in distinguishing between conversion reactions and organic symptoms. The patients were referred to them from a neurological service wherever a conversion reaction was considered in the differential diagnosis. Each patient and his relatives were interviewed and the post-medical records were studied. A prediction was then made of the eventual diagnosis using each criterion individually and together.

Three of the eight criteria turned out to be highly predictive of the existence of a conversion reaction. One was the prior use of physical symptoms as psychological deference. For example a woman who had three attacks of light hemiparesis during disruptions of her three love affairs. Other patients in whom presenting symptoms developed after a marked change in their life circumstances. As an example, a woman in her late fifties recently retired whose life for over 30 years was centered about her work. He first conversion reaction occurred after a rebuff from her physician who was then her closest human contact. Twenty-six of the 32 patients with conversion reaction were positive for this criterion.

Another criterion was the presence of significant emotional stress prior to the onset of symptoms. For example eleven of the patients had immediate or impending object loses, most of which resulted in considerable life changes for the patient such as increased boredum, increased expectations to cope with, impending marriages, increasing sexual intimacy in an important relationship, or during intense family battles. Many of these stresses were clearly significant. Equally important were those circumstances which changed the patients usual defenses.

The third criterion in the predictive index was evidence that symptoms were used to solve conflict brought about by precipitating stress. Usually its purpose was to achieve a secondary gain. An example of this cited was that of a lonely housewife who developed hemiparesis when her only child moved to a distant city. She became helpless, forced her daughter to return to care for her and then gradually the patient recovered. One patient with organic illness used her symptoms to avoid sexual relations with her husband. This indicates that persons with organic illness can also develop conversion reactions for secondary gain.

Other factors mentioned as helpful by different workers such as hysterical personality, "la belle indifference," hysteria, presence of a model for symptoms and expression of symbolism in the symptom, did not materially contribute to the predictive index. By classifying their patients on the basis of the major criteria used above conversion reactions were diagnosed in 93% of the patients. Without employing the predictive index 29% of the patients with organic illness were mistakenly predicted to have conversion reactions.

The results indicate that the criteria comprising the preditive index can be useful in diagnosing conversion reactions. But the necessity remains that organic illness must be ruled out regardless of how compelling the patient fits the psychiatric picture of a conversion reaction. Only seven per cent of the patients who did not meet the criteria set up for determining a conversion reaction later proved to have this diagnosis. Therefore if we learn to evaluate a patient by the predictive index of the three criteria set up by Raskin and it proves to be negative one has ruled out a conversion reaction with a high degree of probability. This can be of considerable help to a physician and may change his attitude.

What has come out of Raskin's study is that conversion reactions often occur as acute psychogenic illnesses with a good prognosis in patients who are not chronic or frequent "users" of somatic symptoms. In the study reported one-third of the patients with conversion reactions were not suffering from "hysteria." Conversion reactions were seen in patients who had functioned well until circumstances drastically changed their adaptation. Those newly widowed or jobless developed somatic symptoms for the first time and this was frequently late in life. Other patients coped with numerous stresses without falling ill but had difficulty with one area of life, such as romantic relationships and developed repeated conversion reactions whenever such relationships were encountered.

As physicians we must never forget organic disease as a source to confuse our appraisal of a conversion reaction. Psychiatrists are also physicians who must be on guard to discover the possible presence of organic disease either as a diagnosis in itself or a basis for the development of a conversion reaction.

L.H.N.

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Problems Of The Noise Deafened Person

The most common complaint of the person with noise induced deafness is "I can hear but I don't understand." His difficulty of discriminating speech is in fact due to intelligence and habit which play a large part in filling in for sounds that are not heard. Dougherty and Welch [1] point out that much of the amplitude (intensity) of speech is low frequency sound heard with the vowels, whereas the understanding of speech is dependent upon high frequency sound carried by the consonants. Thus the nerve deaf person will hear speech of normal loudness but impaired clarity. The first sounds to be lost are the fricative sounds such as f, s, th, ch, sh. This makes difficult the discrimination of words like si*ck*, fli*ck* or chi*ck*.

With greater hearing loss the explosive consonants such as b, t, p, k and d are impaired. It is difficult for the normal ear to appreciate this problem. The simple example Dougherty and Welch give illustrates the difficulty to the deafened person.

The normal person will hear "our offiice is on the twelfth floor."

The severely impaired person will hear our o--i-e - on -e -wel-tt -loor.

The moderately impaired person will hear our o-- i - e -i -- on the twel - th -loor.

The sentence normally would be heard without distortion. The difficulty in discriminating distorted speech in one sentence is bad enough. The problem of a deafened person who has another sentence immediately following can be imagined.

Another problem in noise deafened people is the phenomenon of recruitment (abnormal loudness). When speech or other sound is presented at levels not disturbing to the normal ear, some nerve deafened persons will complain that it is too loud. Thus in a noisy environment, a shout above the noise may be very uncomfortable. In a quiet area, a person with severe loss may encounter the same difficulty when he attempts to utilize a hearing aid with high amplification. He raises the volume of the hearing aid to produce speech of sufficient intensity to be preceived and finds the rapid rise in loudness makes the sound uncomfortable.

Even ordinary background noise will decrease speech discrimination of the nerve deaf. The normal ear shows a sharp decrease in accuracy when forced to discriminate speech above background of 80 decibels. The nerve deafened person finds it very difficult to analyze speech because the high frequencies are often blocked by background noise and it is the high frequencies they barely hear in a quiet environment. It is in the noisy environments usually in loud groups or noisy vehicles where they first notice their hearing loss. Understanding speech becomes difficult, they concentrate for as many cues as possible, they cannot relax or converse and so much effort becomes necessary that they soon complain of fatique.

Some people may understand the problem of hearing for such people in a noisy environment. Few however conceive the basis for hearing one sound yet ignoring another, as for example hearing conversation but ignoring a ringing bell. Yet coworkers and families must learn to accept unexplained variations in the nerve-deaf persons hearing.

Apparently hearing aids for sensory deafness are not as successful as one would wish. They are only small private loud speakers that amplify sound over a narrow frequency range. They make speech louder but do not clarify distortion especially in the persons with a wide difference in perception of high and low frequencies. This is the reason why success with a hearing aid cannot be reliably predicted and why a trial wearing of different aids is a necessary test of their value.

In all cases speech reading is a valuable tool for the severely deaf person. In fact all profoundly deaf persons spontaneously utilize speech reading and desperately try to develop this ability to some extent. Only about one-third of the sounds of speech can be visualized but fortunately many of the hard to hear fricative sounds such as f, th, s, ch are also the most visible. The auditory gaps in the sentence mentioned above—"our office is on the twelfth floor" can be repeated in the mirror and the patient notes the lip movements. After instruction on speech reading a deafened person will find it easier and less fatiguing to discriminate conversation. As physicians become aware that speech reading instruction should be provided, then application of speech reading to all forms of deafness will be encouraged and the older person with slowly progressing sensory loss will not be neglected.

It is astonishing how long it has taken us to recognize that community noise exposure is often above maximum standards established for industry. Heretofore community noise has been a short term exposure as compared to the eight hour period in industry. Now as the power use of both home and street increases it is mandatory that steps must be taken to limit the noise output. Otherwise total timed exposures will exceed industrial standards, standards that rely on regular audiograms to prevent hearing loss by noise defenders and removal of the victim from the noisy environment.

Add hearing loss due to noise and that caused by arteriosclerotic vascular disease and we are confronted with an aspect of preventive medicine heretofore neglected. Health departments and community planners must give special attention to

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*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

Indications: 1. Functional fatigue such as that often associated with: a depressing life experience or stressful time of life; advancing years; convalescence; limited activity or confinement. 2. Poor appetite and vitamin-mineral deficiency as they occur in: patients having faulty eating habits; geriatric patients who are losing interest in food; patients convalescing from debilitating illness or surgery.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

Side effects: Reports of overstimulation have been rare. Patients who are known to be unduly sensitive to the effects of stimulant drugs should be observed carefully in the initial stages of treatment.

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noise hazards where people congregate. In considering the prevalence of hearing loss in the elderly and its pernicious effects, these people deserve particular emphasis in noise control, for they not only run the risk of further hearing loss, but also carry the burden of discriminating above annoying background noise.

Many areas of the community such as subways, other forms of transport, unmuffled motorcycles and automobiles could achieve large reductions in noise with careful engineering, and also if the willful noise producers develop a respect for other people. To reduce noise levels in the kitchens and on the street will require an educated demand by the consumer. Public concern must also be developed to achieve a reduction in community noise hazards for most noise sources can and will be controlled if the individual understands the pernicious effect of noise upon himself and his fellow man.

L.H.N.

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Man's Relationship To His Intestinal Bacteria

We urgently need a much better understanding than we have concerning man's relationship to the bacterial population present in his intestinal tract. For example we do not know what the mechanism is for hypoproteinemia often seen in patients with excessive growth of microorganisms in the small bowel lumen. It is known that malabsorption is induced by small intestinal bacteria but many observations relative to this at present are entirely unexplained. Why do so many patients with multiple jejunal diverticula have no significant absorptive defects. Why are tetracycline and other absorbable antibiotics usually so much more effective than non-absorbable agents such as neomycin.

Why is it that single short courses of antibiotic therapy in cases of malabsorption are often followed by prolonged clinical remissions associated with essentially normal absorption tests? It is apparent that what is urgently needed is a much better understanding of man's relationship to the bacterial population present in his gastrointestinal tract.

The past decade has witnessed intense renewal of interest in these problems. There has emerged a clear concept that the enteric bacteria constitute an important part of the hosts environment. The enteric bacterial role in nutrition, resistance to infection, shock, hepatic decompensation, strangulation, obstruction of the intestine and the response to irradiation has already received much attention. Salem et al [1] have described a patient with scleroderma in whom intestinal malabsorption was associated with prololeration of bacteria in the small bowel.

Studies by Dixon [2] suggest that the mechanical cleansing effect of normal intestinal peristalsis is an effective mechanism by which bacterial growth within the small bowel is limited. Accordingly any disorder in which orderly flow of gut contents is impaired may result in rapid bacterial proliferation and concomitant malabsorption. Poor motility of the gut in scleroderma is probably the basis of malabsorption because of overgrowth of enteric microorganisms. There are other small bowel disorders characterized by impairment of laminal flow and concomitant bacterial overgrowth such as surgical blind loops, diverticula, structures, entero-enteric fistulae and poorly functioning gastrojejunostomis.

There are problems involved in studying bacterial overgrowth in the small intestine. Bishop [3] has found at least 20 bacterial species from blind pouches of the small bowel experimentally produced in rats and dogs. This complexity has limited both the number and quantity of bacterial studies in patients with microbial overgrowth and malabsorption. Indeed currently available methods may not even provide a valid indication of the number and kinds of bacteria which actually exist within the small bowel lumen.

The most common clinical features of small bowel bacterial proliferation are macrocytic anemia associated with megaloblastic bone marrow and low serum levels of vitamin B_{12}. This anemia is correctable by administering B_{12}. The anemia in patients with surgical blind loops and small bowel divertica must therefore be due to bacterial overgrowth which inhibits absorption of B_{12}.

There is as yet no precise explanation for the manner in which the proliferating bacteria in the small bowel interfere with B_{12} absorption. In rats with experimentally formed small bowel blind loops, the malabsorption of B_{12} is corrected by broad spectrum antibiotics or by surgical excision of the pouches. The probability is that the intraluminal microorganisms directly compete with the intestinal cell for the uptake of the vitamin thereby making it unavailable for absorption. This may not be the whole explanation since normal absorption from the bowel has been noted to occur in the presence of massive contamination with bacteria.[4]

Another observation is concerned with fat absorption during bacterial overgrowth in the small bowel. One-third of such patients show steatorrhea. This could not be attributed to competition by bacteria for fat since only one per cent of lipids is found bound by bacteria. The syndrome of steatorrhea is generally moderate. In experimental animals fecal excretion of fat can be increased by blind loops and as in anemia abolished by broad spectrum antibiotics. Here the malabsorption of dietary fat is not due to impairment of absorptive power of the intestinal epithelium. Perhaps as the work of Donaldson and others have shown, the explanation can be found in alteration of bile salt metabolism and resultant inadequate preparation of the fats for absorption.

There are some positive values to the presence of microorganisms in the bowel. It has been understood for a long time that fully grown cultures of viable microorganisms do not readily permit a newly introduced strain to flourish. In the gut there are relatively large resident bacterial populations which could interfere with newly introduced microorganisms whether pathologic or not. These will multiply only when applied in large numbers or when the underlying flora have been reduced in numbers. Thus it is difficult to establish shigella or salmonella in the gut of man or laboratory animals unless relatively large numbers of bacilli are ingested.[5]

Conversely antibacterial drugs may reduce the number of organisms in the gut and permit the ready implantation of a few pathogens or other new organisms. Perhaps Metchinkoff would have had greater success with his desire to prolong life by substituting lactic acid bacilli for the usual intestinal flora if he had access to broad spectrum antibiotics. And how thankful should we be to the existing intestinal flora for being spared more salmonellosis that we contract, considering the widespread distribution of salmonella organisms in our food supply.

L.H.N.

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Circadian Clocks: 24 Hour Rhythms In Man

Throughout our lives we experience an alternation of light and darkness with an almost constant cycle length in 24 hours. This fixes our pattern of behavior with periods of sleep, activity, meals etc. Many of our habits are also affected by circadian periodicity and many of our physiological functions display the same rhythmic behavior.

Certain epidermal tissues exhibit rates of cell division peaking in the late evening and coinciding with the nocturnal sleep habit. Hemoglobin concentration, red cell count and size, plasma proteins all show high values by day and low values by night. The vital capacity of normal healthy men falls rapidly just after midnight, a change probably due to increase in total blood content in the lungs. The temperature shows lowest values in early morning and this variation is not due entirely to muscular activity during the day because the same is found in patients confined to bed.[1]

One of the best studied circadian oscillations is the renal excretory rhythm which shows a peak urine flow during the day with a minimum at night. This may be related to a circadian rhythm in the activity of the adrenal cortex whose hormones control kidney function and regulate water balance by causing sodium and chloride retention and excretion of potassium. Cortisol secretion periodicity must also effect carbohydrate metabolism, behavior of membranes in the joints, eyes, skin and elsewhere.

Circadian rhythms in normal man will persist indefinitely unless the subject changes his habits in which case they may become desynchronized as happened to three normal subjects who spent several months in a cave[2] or as happens when one flies from this country to Europe and back. The rhythms can, however, resynchronize after the return of the subjects to their normal societal life. Circulatory rhythms can be desynchronized by disease, as happened to a child with recurrent fever in whom the blood pressure underwent a circadian rhythm deschronization from its 24 hour "Clock".[3]

A knowledge of the normal cycle can provide a context within which to measure the disturbance caused by disease. For example, we are accustomed to regard a high nocturnal urine flow as an indicator of disease. Acute lesions of the kidney tubules can cause a very large circadian variation in blood pressure which subsides during recovery. This means that if we record blood pressure at the time of its peak we can readily measure progress of the disease rather than if the readings are taken at random times of the day.

The information on circadian systems has possible therapeutic relevance and awaits further study. Experiments on animals already have revealed that the effect of an overdose of Ouabain as well as that of a potentially noxious agent is a function of the circadian system phase at the time of the administration of the agent. Mortality from an identical

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dose of toxin given to mice may exceed 80% at one time of day and fall to about 20% at another.[2]

Circadian rhythms may be causally related to disease if the occurrence of pathology is aided by a critical physiological change. Human beings seem to be more vulnerable during the night to cerebral hemorrhage, pulmonary edema and cardiac asthma. Periodicity in psychoses is well documented in a case report of a patient who had a regularly periodic occurrence of psychotic episodes.[4] When he was placed on an abnormal time schedule the period of the psychosis was altered even though other physiological activities such as renal function adhered to a circadian cycle.

The real problem is whether some disease processes can originate in the disruption of normal phase relations between circadianly varying functions. Such an event has been shown in kidney function.[5] If phosphate buffer is given it will increase excretion of acid by the kidney. Both acid and phosphate excretion peak normally at night. These facilitate each others action. If, however, the two oscillations become desynchronized severe symptoms in the urinary tract can develop.

There is much evidence[3] that circadian rhythms have an internal origin resulting from the functioning of a endogenous "clock" rather than merely being a response to periodic changes in the environment although background radiation, geomagnetism, the earth's electrical field[6] and light, have received much attention. One reason is that a rhythm might not have its own clock but might instead be controlled by some other function which has its own circadian timekeeper. Such a circumstance is seen in the fluctuating level of eosinophiles in the circulation. Their level is under control of cortisol whose secretions is in turn mediated by 24 hour variation in ACTH which is itself controlled by feedback from cortisol blood levels.[7]

The complexity of the relationships between clocks is made apparent if we begin at the cellular level. Each separate cell and each member of a chain of glandular organs can have an intrinsic circadian rhythmicity which is either inherent or developed and sustained by environmental periodicities. For this reason it has been difficult to decide whether or not some experimental procedure is influencing a "clock" directly or acting as a factor somewhere along the line in a causal sequence. If one gives potassium salts at night it will alter electrolyte balance sufficiently to disrupt the normal circadian rhythm, but when potassium is withheld the normal oscillation returns. On the other hand reserpine will upset the normal temperature rhythm and when the oscillation returns after reserpine is cut off the rhythm is out of phase.

One of the most extraordinary phenomenon connected with circadian oscillation is the relation between a human host and the infesting parasite Wucheria bancrofti. It appears the infesting organism adjusts to the hosts temperature variation entering the skin when the temperature is low and retreating to the lungs when the temperature is high. It is probable that some organisms cannot survive a high temperature of the host and this may be an important factor in immunity. Perhaps when a temperature is low the conditions are right for an invading organism to begin multiplication.

As the field of knowledge in 24 hour rhythms expands it could have immediate applications in the daily practice of medicine.

L.H.N.

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If We Can Persuade Our Patients Not To Smoke

Respiratory system disease including malignancy is now a most important cause of death in man. Such illness was responsible for 12 per cent of the male deaths in California in 1960. If as Hammond has logically suggested, many deaths signed out as due to coronary artery disease are in fact significantly contributed to by underlying fibrosis or emphysema of the lungs, then the true proportion of male deaths basically due to respiratory disease may be much greater perhaps nearly 1/4 of all deaths. The deaths in women in the major cardiorespiratory disease categories are half that of men and in pulmonary emphysema 1/7 of men. These different ratios are perhaps due to lesser exposure of American women to cigarette use.

If smoking is associated with a high incidence of respiratory disease and cancer then one should find low mortality and low morbidity among non-smokers. Such a study has first been reported by Lemon and Walden[1] among Seventh Day Adventists (SDA) who are essentially non-smokers. Two per cent were currently smoking, 65 per cent had never smoked, whereas among controls 59 per cent were smokers and 21 per cent never smoked.

The important finding as might have been expected[2] is that SDA mortality from all causes, all types of cancer and coronary artery disease was half of that expected and the most outstanding deficits were found in those diseases closely related to the respiratory tract. Fifty six cases of cancer of the lung were expected and only nine found. There were no deaths from cancer of the mouth, or larynx whereas 19 were expected. Whereas 134 deaths from respiratory tract disease were expected only 43 were found. One case of tuberculosis occurred and 19 were expected. Nineteen pneumonias were observed and 68 were expected. Bronchitis and emphysema were observed in 5 vs 25 expected. Altogether an expected 898 SDA deaths did not occur during this five year period!

The authors carefully analyzed other factors that may have contributed to the striking reduction in mortality such as socio-economic advantage as related to occupation, rural vs. city, but these played no role. It is a sobering fact that this epidemic disease is extremely rare among non-smoking life time SDA members whatever their occupational, residential, or other environmental exposures.

The authors carefully considered two possible biases in their conclusions but found them inoperative. One was that the expected death rates in other Californians were made too high and another that not all deaths in the SDA population were accounted for. It must therefore be faced that the profound and broad effects of the many toxic substances in the cigarette (including the mucotoxins and polonium 210) on the physiological mechanisms of the body particularly the vital cardiopulmonary and circulatory systems should be expected to have a similarly profound effect on the mortality patterns related to those systems.[3,4,5]

Many SDA's have a better economic status than do their fellow Californians. They are a more literate educated, economically able population with known interest in health matters. But such factors appear negligible compared with results of the abstinence from tobacco. Neither could the authors find selection or "constitutional" theory of lung cancer as an explanation for the lung cancer in smokers as against non-smokers. Many are vegetarians avoid tea, follow a way of life which includes adequate rest, recreation, exercise, avoidance of tension and worry, good hygiene and prompt co-operation with medical care. What part such hygiene plays in lowered respiratory disease mortality if any, is not yet known.

In the search for other rational explanations for the current lung cancer epidemic in the United States and now the epidemic increase of pulmonary emphysema and bronchitis, air pollution has been suspected. A careful analysis of the figures presented by Lemon reasonably rules out this factor as a cause. The belief is justified that lung cancer would decline as a significant death risk if cigarette smoking ceases in this country.

SDA men are almost certainly experiencing a preferential longevity and the chief reason for this selective advantage in cardiorespiratory mortality is due to their abstinence from the use of tobacco particularly cigarettes. The probable longevity associated with this decreased risk of death among non-smoking SDA's is itself striking. It has been estimated in these Columns[2] that a smoker of 20 cigarettes a day has a reduced longevity by eight years and if he smokes 40 cigarettes a day his life expectancy is reduced by sixteen years. Abelin[6] in a recent life table analysis of smoking study data, indicated in confirmation of the above figures that if one assumed a causal relationship between smoking and higher death rates, then increases in longevity resulting from non-smoking might equal the whole of that achieved in the last 40 years with all the progress in medical Science!

While the hunt goes on in many quarters for a "safe" cigarette, it is important to notice again that the knowledge is already at hand for ending the epidemic of lung cancer and reducing the growing problems of cardiopulmonary crippling and untimely deaths from emphysema and coronary artery disease. The studies among SDA's warrants the conclusion that male longevity in this country could be significantly increased with a corresponding decrease in morbidity and mortality from cardiorespiratory disease of all sorts if cigarette smoking were to become an unacceptable social habit.

It should be a matter of considerable scientific interest in itself why cigarette smoking continues unabated despite the mountainous evidence of its hazard. This widely indulged and perilous habit is little restricted by government action, public health leadership or individual responsibility of a person to himself or his family.

L.H.N.

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The Cell: New Light On An Old Problem

The concept of the cell as the unit of biological structure both in plants and animals is an old one since the time of Schleiden and Schwann. More than 100 years ago Virchow established the cellular basis of disease. The cell image we inherited from preceding generations of biologists was that of a droplet of relatively homogeneous glossy substance or "hyaloplasm" with a nucleus and a few granules inside. And yet we know this could not be so since cells varied so widely in their function from nerve transmission, to contraction, to urine formation, to secretion and many others.

Cells now since the introduction of the electron microscope, have turned out to be much more elaborately organized than previously assumed, the salient finding being the remarkable amount of compartmentalization of both animal and plant cells and this is accomplished by the extensive use of intracellular membranes. So now we have a new image of the cell which is evolving since the middle 1950's namely a conglomerate of compartments separated from one another by membrane partitions. It is truly a membrane box containing within it a series of smaller boxes each bounded by its own membrane and each occupied by one or more distinct components (particles, fibrils, matrix) often unique in their distribution. The variability of all cells in animals or plants rested upon an obviously common pattern of organization. They were variants on a common central theme. Only the bacterial cell was without compartmentalization.

All this knowledge has come to us first as a result of our ability with the electron microscope to visualize small objects by 400 times greater magnification than with the light microscope. But special fixing techniques were necessary to prepare tissues for the electron microscope. Further just seeing what the structures looked like was not enough. It was necessary to develop techniques of cell fractionation, radioisotope uptake and autoradiography in order to correlate at the molecular level the structures within the cell with their biochemical activity.

It was for this brilliant achievement that G. E. Palade was awarded the Albert Lasker Basic Research Award. The gradual steps in observation, experiment and brilliant intuition which led him and his group to clarify the structure and function of the cell—"the wonders of life" is described in a recent issue of the J.A.M.A.[1]

The first discovery was that of a small particle called ribosome, some free in the cell, others attached to a membrane of a microsome. The ribosomes were found to contain ribonucleic acid which is known to be involved in protein synthesis. We have long known cells synthesize protein rapidly either for growth or secretion now we know this is performed by the ribosomes.

By cell fractionation it was possible to obtain for study another subcellular component, the microsome, a fragment of the endoplasmic reticulum with a rough surface to which the ribosomes are attached. By means of radioactive amino acids it was found that they became more actively incorporated into the protein of microsomes, than in other cell fractions and the radioactive proteins became mostly concentrated in the ribosomes. It then turned out that the ribosome free or attached is the site of protein synthesis. The process involved a number of factors i.e. amino acids activating enzymes, transfer RNA's amino acid transferases and polymerases, all of them present together with the ribosomes in the same cell compartment—the matrix or cell sap. Then messinger RNA was added to the list of factors and out of this emerged a concept of polyribosomes—that ribosomes occur in clusters.

Thus Palade started with the discovery of a new particulate component by electron microscopy, isolated the attached and free particles from microsomes and cell sap respectively, characterized them biochemically as ribonucleoprotein and then demonstrated their ability to synthesize proteins when properly supplemented. Several gaps in knowledge remained such as relationship between free and attached ribosomes, the functional meaning of the endoplasmic reticulum (E.R.), and others as well.

Using the pancreatic exocrine cell which produces a number of digestive enzymes and zymogens and the method of autoradiography they were able to formulate a general hypothesis every step of which was finally verified: secretory proteins are synthesized by attached ribosomes, they are then transferred across the membrane of the rough E.R. into a cisternal space and then into condensing vacuoles. Here they are concentrated and become zymogen granules and stored temporarily in the apical region of the cell.

This structural-functional correlation as described in the work on the pancreatic exocrine cell showed that extensive and varied transport operations take place at the subcellular level from cell compartment to cell compartment, many of these phases such as massive transport of protein from attached ribosomes to the cisternal space, the transport of proteins from the attached ribosomes to the condensing vacuoles and the movement of membranes to the cell surface are of course involved in the formation and discharge of zymogen granules. These complex processes involved in external secretion, also occur with some modification in the appearance and accumulation within the cisternal space (vacuoles) of amorphous products in many other types of cells.

It should be clear to all of us why Dr. Palade was honored by the Lasker award. With imagination and high technical skill "he travelled into new land and became its chief geographer." (See page 140 for review of Fawcett's book on the Cell.)

L.H.N.

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Fluoride And Osteoporosis

There are widely separated areas in the United States in which osteoporosis in the population varies inversely with the fluoride content of the drinking water. In Bartlett county Texas the fluoride content of the water is 8 ppm. The people here showed substantially less osteoporosis than residents of Framingham, Massachusetts where the fluoride content of the water is .09 ppm. These two communities however are far apart and vary in climate, diet and possibly racial origin. It however raises the question whether the prevalence of osteoporosis in more comparable communities varying only in the fluoride content of the drinking water would show a similar inverse relation between osteoporisis and fluoride intake from drinking water.

Bernstein et al[1] found just two such communities in North Dakota with people of the same stock and dietary habits but one drinking water from artesian wells containing 4.6 ppm fluoride and another in which the drinking water was low in fluoride content (0.15-0.3 ppm.). They found that the prevalence of osteoporosis was distinctly higher in the low fluoride areas than in high fluoride areas both in men and women. For example collapsed vertebra in females 60 or over was high in the low fluoride areas. This they could not attribute to any history of bone disease, age at menopause or obvious gonadal findings. A greater number in low fluoride areas complained of low back pain especially women. What was especially valuable about these findings was that there were fewer instances of calcified aortas detected in those drinking high fluoride content water.[3]

Bernstein's study indicates the necessity for consideration of fluoride ingestion in assessing the prevalence of osteoporosis. Fluoride consumption in this study appears to have significantly reduced the prevalence of low bone density in women and probably also in men. Those drinking high fluoride water showed decreased prevalence of collapsed vertebra especially with advancing years. These differences could not be attributed to calcium and cholesterol intake since people in the low fluoride areas ingested the same amounts of milk and cheese as those in high fluoride areas.

Since osteoporosis is a disease characterized by an absolute decreased bone mass more pronounced as age advances, any agent which affects progression of the disease is important to recognize and evaluate in terms of its presentive and therapeutic significance. In fluoride we have just such an agent since it appears to help keep calcium deposited in the hard tissues of the body—teeth and bones. It probably does this by inducing crystal growth and perfection in the enamel of teeth. The same process occurs in hydroxyapatite of bone. These enlarged and more perfect bone crystals may be less susceptible to resorption and if so they might account for Bernstein's observations.

One incidental finding statistically highly significant in men and potentially of considerable importance was the reduction in calcification of the aorta in both sexes in the high fluoride areas. If the same occurs in other vascular tissues especially the cerebral arteries, then fluoride will indeed become an important preventive measure in two of the main diseases of aging: osteoporosis and arteriosclerosis. With these exciting possibilities that fluoride opens up in preventive medicine we must not forget the proven role of fluoride in lessening tooth decay by 60-70 per cent if the community drinks fluoridated water.[3]

L.H.N.

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Leiomyosarcoma Of The Inferior Vena Cava

John A. Gariepy, M.D., and Russell H. Pope, M.D.

■ Smooth muscle tumors of veins are rare enough so that when such a case is discovered it is frequently reported as a single case history. Cheek and Nickey[2] reported twenty-two such cases in the most recent review of this tumor. Of the twenty-two such cases, thirteen included a leiomyosarcoma which involved the inferior vena cava. Additional cases have been reported of leiomyosarcomas involving other major veins such as the femoral, saphenous and the external jugular. The first reported case of a sarcoma of the inferior vena cava was that of Perl[7] in 1871.

The first reported case of resection in an attempt to extirpate the tumor was reported by Cope and Hunt in 1954.[4] In their case the leiomyosarcoma involved the inferior vena cava below the renal veins. The tumor and the inferior vena cava were excised. Recurrence of the tumor occurred sixteen months later. This current case report presents several interesting features in addition to the fact that it is a rare tumor. It is the second reported case of leiomyosarcoma of the inferior vena cava which was resected for cure. The patient had the longest interval between the primary resection and the first recurrence of the tumor. The patient received a therapeutic modality which had not been used previously for the recurrences of such tumors involving smooth muscles of major veins.

Case Report

The patient, a 47 year old female, was first admitted to Bridgeport Hospital in September 1959 because of right upper quadrant pain. G.I. series and gall bladder studies were negative. An IVP was also reported as normal. The urologist believed he was able to palpate the lower pole of the right kidney. Because of negative studies and a negative physical examination the patient was treated conservatively for this pain which appeared to spontaneously subside.

The patient was readmitted to Bridgeport Hospital in October 6, 1960 because of severe subcostal pain radiating under the right scapula. The pain which had been intermittent in the past had become steady in nature prior to the present admission. There was no history of fatty food intolerance and no episodes of jaundice, or acholic stools. The past history was negative except for a routine appendectomy and hemorrhoid-ectomy. There were three normal pregnancies. On physical examination there was a mass palpable in the epigastrium which extendeed to the right of the midline. The mass was about the size of an orange. It was not tender to palpation. Pelvic and rectal examinations were negative. Examination of the extremities revealed no edema. There were no varicosities of the peripheral veins. There was no evidence of distended veins suggestive of venous collateral circulation of the lower trunk. Admission blood and urine examinations were normal. The icterus index was 7.2, alkaline phosphatase was 2.22 Bodansky Units mg.%; phosphorus 3.11ml%; amylase 18 units; pyruvic transaminase 14.

Once again the gall bladder series, G.I. series and IVP were normal; the barium enema was negative. On October 11, 1960 an abdominal exploration was carried out through a right para-median incision. A large tumor could be palpated in the retroperitoneal space behind the duodenum. A Kocher maneuver was performed on the duodenum to reflect it to the left. There was no evidence of metastatic disease of the liver. The tumor occupied the space between the gall bladder and the right kidney. (Fig. I) Circumferential dissection was carried out around the mass, which then appeared to arise from the inferior vena cava, and below the right renal vein. The vena cava was divided below the renal veins and at the level of the common iliac veins. The mass was not attached to the aorta and could be removed en bloc. Postoperatively the patient had slight ankle edema which was treated with elastic stockings. There was also a suggetsion

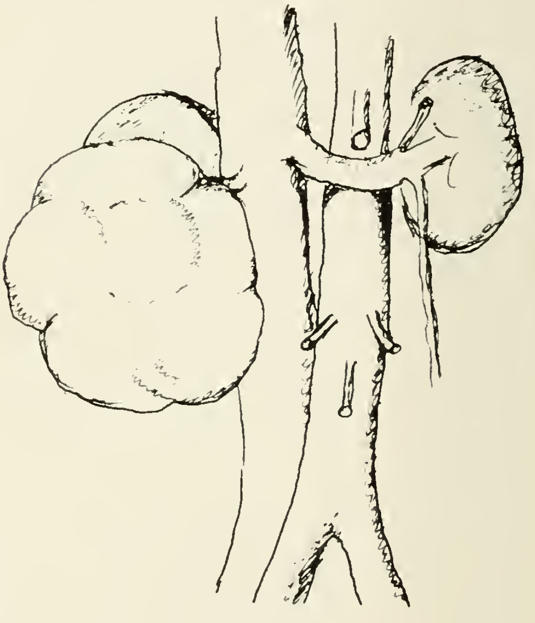

FIGURE I

This is a schematic drawing of the tumor in situ.

DR. JOHN A. GARIEPY, associate attending surgeon, Bridgeport Hospital, Bridgeport, Conn.

DR. RUSSELL H. POPE, chief pathologist, Bridgeport Hospital, Bridgeport, Conn.

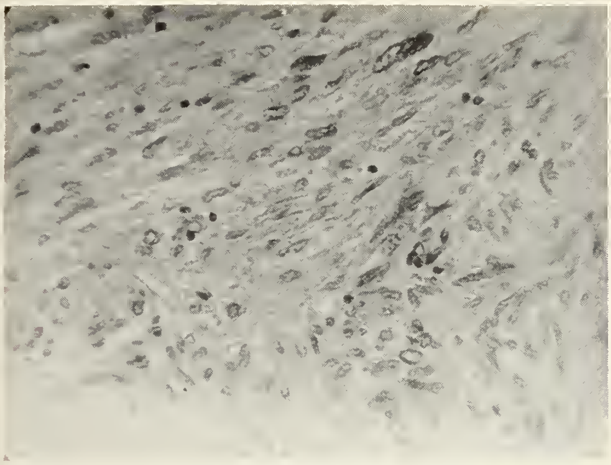

Figure II
This picture shows the characteristic appearance of most of the tumor consisting of interlacing bundles of smooth muscle cells. X 400.

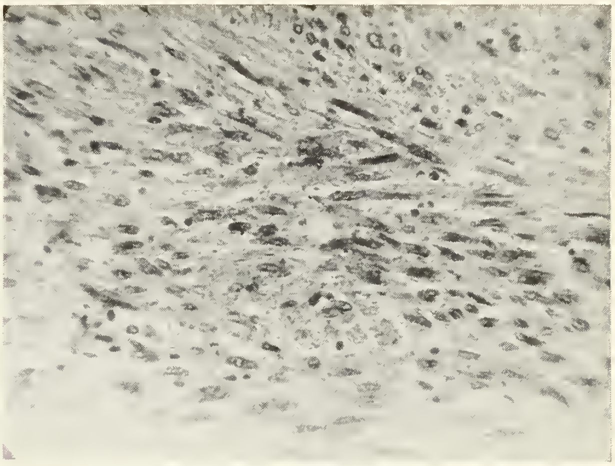

Figure III
In this area the tumor nuclei are more irregular and bizarre. X400.

of transient superficial thrombophlebitis; otherwise, her post operative course was essentially benign.

Pathology

The specimen consisted of a large, thinly encapsulated, lobulated mass measuring 15 x 13 x 10 cm. Several veins stretched over the capsule, and in one area there was a segment of vein wall, probably inferior vena cava which blended into the large tumor mass. On section, the tumor presented a homogeneous, gritty, pale pink tissue with whorl-like fibrous streaks throughout. It had the appearance of a cellular leiomyoma. There were small foci of hemorrhage and cystic degeneration in areas. Microscopic examination revealed interlacing bundles of cells and fibers. (Fig. II) The cells were spindle shaped and occasionally had fairly large amounts of pink cytoplasm. Most of the nuclei were small, uniform, ovoid structures but an occasional nucleus was large, lobulated and coarsely granular. (Fig. III) In these latter areas, up to 5 mitoses could be seen in one high power field. In one section, the tumor was protruding into the wall of the large vein with the intima and the muscle coat of the vein fusing into the tumor. (Fig. IV) A small lymph node in one section did not demonstrate tumor cells.

Post-operative Follow-up

The patient was completely asymptomatic until May 1965. At this time she began to develop symptoms similar to those which she originally had. There was pain in the right lateral subcostal region.

On physical examination there was hepatic enlargement of the right and left lobes of the liver. The liver edge was palpable about 4 cm. below the costal margin. In addition there was a 2 cm. freely moveable mass in the subcutaneous tissue at the left costo-phrenic angle.

A biopsy of this mass was performed and the microscopic examination revealed a leiomyosarcoma similar to the previously excised tumor.

The patient was readmitted to the hospital; all diagnostic X-rays were again negative. The only

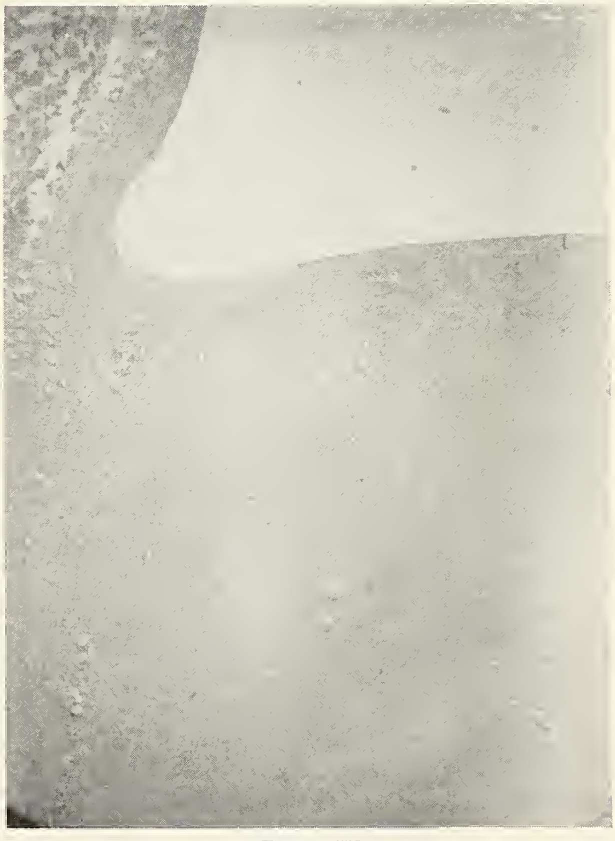

Figure IV
Low power view of leiomyosarcoma arising from the wall of the inferior vena cava. X 80.

abnormal laboratory test was an alkaline phosphatase of 10.5 KA units. On this admission a liver scan was performed using radio-active Rose Bengal. This revealed evidence of tumor replacement in the right and probably the left lobes of the liver.

Since this lesion is generally considered radio resistant the patient was referred to Dr. George Pack in New York. An exploration was performed June 28, 1965. Numerous metastatic liver deposits were seen. A retroperitoneal mass was also palpable in the area of the right renal vein. A polyethylene catheter was placed in the right gastro-epiploic artery and guided into the hepatic artery. The gastro-epiploic artery was then brought to the skin surface with the catheter sutured in place, ceramic microspheres measuring 50 microns in diameter and containing radioactive yttrium^{90} were injected into the catheter. A total dose of 75 millicuries was given in this manner. In addition she received Vincristine 1.5 mg. intravenously at various intervals. Prednisone 5 mg. three times a day was also used. Finally, cobalt therapy was added. Over an anterior port 13 x 22 cm. which encompassed the portal fissure and at a target skin distance of 70 cm., 3000 rads were administered in fractionated doses. The patient had an intense skin reaction.

Following therapy in New York the patient experienced severe anorexia which was attributed to massive radiation. In September 1965 she was admitted to Bridgeport Hospital after passing tarry stools mixed with bright red blood. Her hematocrit was 31 with normal white blood cells and platelets. The bilirubin was normal. The alkaline phosphatase was 28.1 KA units. The prothrombin was normal. The initial impression was that marrow depression was causing bleeding, however, bleeding and clotting studies were normal. The patient received fresh and bank blood and the bleeding stopped. She remained in the hospital for a month receiving supplemental intra-venous fluids until she was able to take a reasonable diet. During her hospitalization she complained of heartburn and right subcostal pain radiating to the back. For these symptoms she was treated with analgesics and anti-acids. The liver was still palpable 4 cm. below the costal margin.

The patient remained at home for a month and then was readmitted to Bridgeport Hospital because of massive gastro-intestinal bleeding. Seven units of blood were required to control the hemorrhage. Once again laboratory studies were normal except for an alkaline phosphatase of 21.8 KA units. After a week of conservative management a gastro-intestinal series was planned. However, on the day before, the patient again had massive bleeding. The bleeding continued for 24 hours without evidence of stopping. Therefore, the patient was taken to surgery. The abdomen was explored through a midline incision. Large masses were palpable in both lobes of the liver. The pylorus was fixed to the anterior abdominal wall by a thin cicatrix. Therefore a gastrotomy was performed. Examination of the pyloric channel revealed dense scar circumferentially and a suggestion of a posterior wall crater. At this time the examining finger perforated the wall, and massive uncontrollable hemorrhage began. The area was packed with sponges and the operation terminated. The patient expired twenty hours later from continued hemorrhage.

Autopsy examination revealed a large tumor mass involving the hilum of the liver with erosion into the distal portion of the stomach and the portal vein. A large ulcer crater in the gastric wall could be probed directly into the portal vein and the intestinal tract contained a large amount of blood. The left lobe of the liver was studded with metastatic nodules of varying size and the right lobe of the liver was almost completely replaced. Examination of the area of previous resection of the vena cava revealed no gross evidence of recurrence at this site. Microscopic examination revealed tumor replacing the liver similar to that described above. This tumor also infiltrated the gastric wall, duodenum and the portal vein. A solitary metatasis was found in the lung.

Discussion

Leiomyosarcoma arising from smooth muscle of a vein wall is an exceedingly rare tumor. The gastrointestinal and genito-urinary tracts are the more frequent sites of this type of tumor. The clinical symptoms and signs which are produced by such tumors are often quite bizzare.

Overheim and Tesluck[6] described a case in which the tumor originated in the inferior vena cava and extended to the hepatic vein producing jaundice and pain. Exploration revealed a normal patent common duct. Hoffbrand[5] reported a case in which the tumor involved the inferior vena cava and the hepatic veins producing jaundice. In addition the tumor extended up the inferior vena cava where pedunculated tissue acted as a ball-valve in the tricuspid valve causing symptoms of right heart failure.

These tumors which involve the hepatic veins produce a picture similar to that described by Budd[1] and Chiari.[3] Several cases which were reported by Cheek and Nickey[2] describe a tumor which completely obstructed the vena cava. In these patients peripheral edema, ascites, and collateral circulation were predominant. In this present case, and in the case reported by Cope and Hunt,[4] there was no obstruction to the inferior vena cava. Whether or not the tumor grows into the lumen of the vessel or out into the retroperitoneal tissue seems to be unpredictable.

Several interesting observations can be made from this case. In reviewing the literature, this appears to be the second leiomyosarcoma of the inferior vena cava below the renal veins which was resected in an attempt to cure the patient. The first operation was performed by Cope in 1951.[4] Following surgery that patient received 4800r deep X-ray over a three week period. She was reoperated 16 months later for a recurrence and at that time a right nephrectomy was done. Thirteen months later another exploration was performed for local recurrence. At that time a radium pack consisting of 20 mg. of radium needles encased in 0.6 mm of platinum and 1 mm of lead covered with rubber was placed in the operative area. It was removed in 92 hours. This present case was well and without symptoms for five years following local excision. However, when metastasis occurred the spread appeared to be hematogenous to the lung and the subcutaneous tissue in the left costo-vertebral area. External radiation alone has had little effect on these tumors. Therefore, organ infusion was attempted. This form of therapy appeared to have little or no effect in arresting the growth of the metastases. Also of note was the fact that the patient did not develop any peripheral edema following excision of the vena cava with ligation of the vessel just above the entrance of the common iliac veins. The hypogastric veins communicate with the azygous system to prevent peripheral edema when the inferior vena cava is resected. This collateral system appears to work well when associated phlebitis is not present.

Conclusion

Leiomyosarcoma of the inferior vena cava is an exceedingly rare tumor which can present a wide range of clinical signs and symptoms. There has been no reported cure following the resection of a leiomyosarcoma in this area. Five years does not appear to be a sufficient time for follow-up to insure a patient against local recurrence or distant metastasis. Radiation therapy, or organ infusion with radioactive material does not appear to be able to eradicate the tumor. Vincristine had little or no effect on this particular tumor.

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LIMITS OF FINITE KNOWLEDGE

In practical terms . . . our knowledge is finite and never all-encompassing. There is always much we miss, much that we cannot be aware of because the very act of learning, of ordering, of finding unity and meaning, the very power to talk about things means that we leave out a great deal.—J. Robert Oppenheimer. "On Science and Culture." *Encounter,* October, 1962, p. 9.

Basal Cell Epithelioma Complicating A Pilonidal Sinus

Massoud A. Marjani, M.D.

■ Up to the present time the medical literature documents only one case of pilonidal sinus with superimposed "basal cell epithelioma," which was reported by Goldman and Kalow[7] in 1940; this occurred in a fifty-six years old white female who had had pilonidal disease, characterized by intermittent episodes of swelling, inflammation, combined with drainage for one year; routine microscopic examination of the excised specimen showed a basal cell epithelioma arising in the cyst wall, and adjacent sinus tracts.

Recently in Waterbury Hospital surgical service, we were confronted with a case of pilonidal sinus, complicated by basal cell carcinoma, and we were impressed by the fact that it is an unusual surgical problem, and a very rare complication of this fairly common disease. The present article will afford an opportunity to present this case.

Case Report

G. P. a fifty-five years old white woman was admitted in The Waterbury Hospital, on April 4, 1966; she gave a history of having had a discharging sinus over the sacrococcygeal region for over twenty years; this became infected at least several times every year, and drained spontaneously; since two years ago she noticed sanguino-prulent discharge and ulceration, combined with pain and tenderness in the affected area; walking and sitting had became uncomfortable. During all this time she was without medical supervision. Her general health has always been good, with no serious surgical or medical illness, the family history was non contributory.

Physical examination revealed a healthy female weighing 132 lb., her blood pressure was 128 mm. Hg. systolic and 88 mm. Hg. diastolic, respiration 17 per minute, the rest of physical examination was essentially negative, except for local finding: Over the sacro-coccygeal area, 3 inch above the anus, and extending to the right of the midline, there was an indurated, friable, fungating mass with ulceration in the center, and multiple sinus openings with prulent discharge (Fig. 1).

There was no enlarged lymph nodes in the groin or axilla, rectal examination was normal.

On April 6, 1966, under general anesthesia, a very wide local excision of the sacro-coccygeal lesion was performed, and the entire mass down to the gluteal fascia and periosteum of the sacrum was excised, the wound was closed primarily; the patient convalescence was uneventful, healing took place in about two weeks, and she was discharged to tumor clinic for further follow-up.

Pathology Report

Gross examination of the specimen consists of an irregular ellipse of skin, measuring 4 cm. in length and 2.5 cm. in maximum width, the attached underlying fatty tissue measures 2.8 cm. in maximum thickness. In the center of skin ellipse is an area of bony hard gray white slightly raised papillary tissue measuring 2 cm. in length. Cross section reveal the dense gray tissue to extend to a depth of 0.5 cm., in the remaining of fatty tissue there are several large branching sinus tracts lined by dark red granulating tissue.

Microscopic: Segment contain basal cell carcinoma (Fig. II); the tumor is formed of sheets of cells, these have a trabecular pattern in some zones. The cells of the periphery show a pallisading, the majority of cells are uniform, mitotic figures are moderately numerous. Section from margin of the specimen show a clear zone of intact epithelium, and there is no evidence of extensive underlying

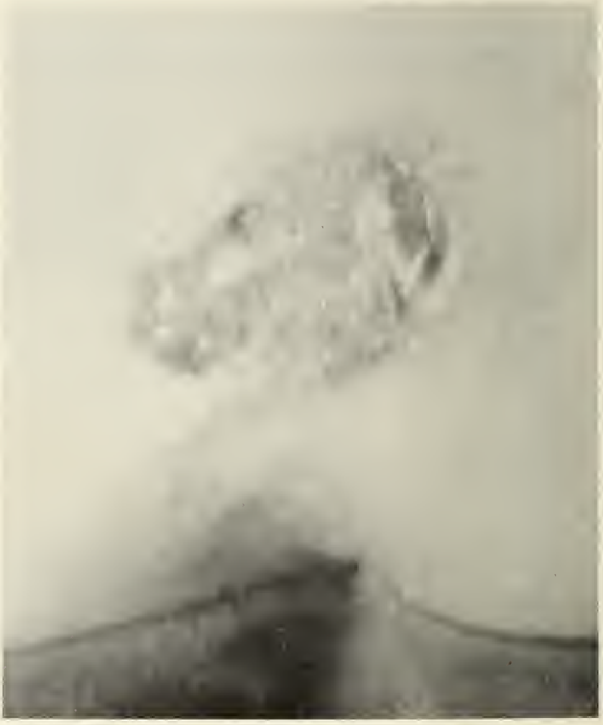

FIGURE I

Basal cell epithelioma arising in the pilonidal sinus, the tumor is extending to the right of the midline. Gross appearance of the lesion prior to excision.

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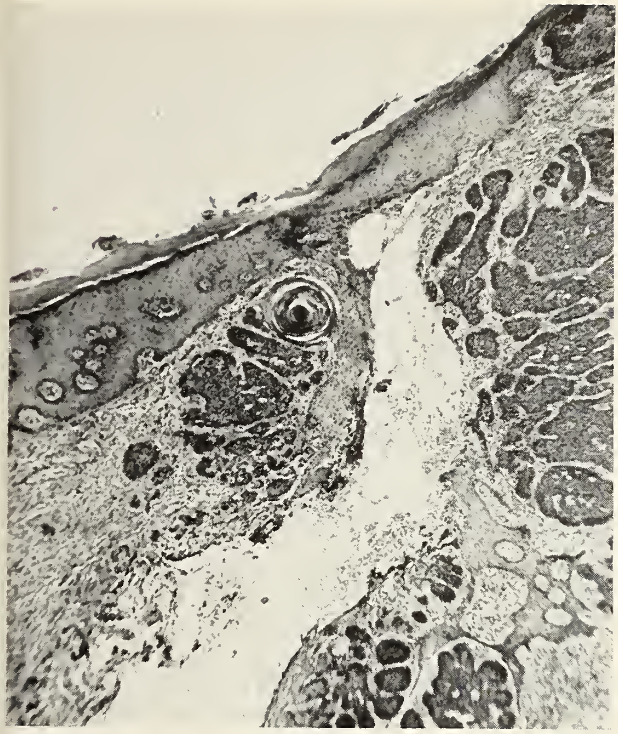

FIGURE II
Microscopic appearance of the lesion: In the center there is a sharply demarcated area of keratotic debris around a sinus tract, basal cell epithelioma with columnar arrangement is in the cells of periphery, there are numerous mitotic figures in the tumor cells.

by the tumor. In several zones there are sharply demarcated area of keratotic debris lying beneath the main tumor mass.

Comments

Malignant transformation in a pilonidal sinus is very uncommon; a summary of the 21 previously reported cases is given in Table I; and it is of interest that the last 13 cases have been reported since 1956; perhaps more thorough gross and microscopic study of pilonidal sinus specimens may reveal a higher incidence of malignancy than has been reported in the medical literature.

No more is known about the etiology of malignancy arising in a pilonidal sinus than about the etiology of malignant degeneration elsewhere in the body; of the various etiological factors associated with carcinoma, the role of chronic irritation as prime factor has long been mentioned in the medical literature,[12] surely a pilonidal sinus that has been draining and intermittently inflamed during several years, and exposed to a great amount of trauma, would be the site of irritation; yet malignant change in such a condition is a rarity.

There are several interesting aspects with regard to management; any patient with pilonidal disease who is troubled with chronic drainage, or recurrent episodes of acute inflammation, should be strongly urged to have surgical therapy; this is particularly true in the patient who has noted any increase in pain, or sanguino-prulent drainage. The surgical procedure in any situation complicated by carcinoma, consists of a wide excision extending at least 4 cm. away from all pathological tissue, and proceeding deeply down to the periosteum of the sacrum and coccyx, and the gluteal fascia.

Summary

The second case of basal cell carcinoma arising in a pilonidal sinus is described, this is the twenty-second instance of carcinoma complicating a pilonidal sinus. Chronicity of the disease in this case was a prominent factor, as in most reported cases. Sero-prulent discharge, pain, ulceration and overgrowth are gross symptoms suggesting malignant degeneration, and they were especially true in our case.

Radical excision provides a good prognosis for such a rare complication of this fairly common disease.

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Table I

Types of Carcinoma Arising in Pilonidal Sinus, Age and Sex, Duration of the Disease and Authors as Reported in the Medical Literature:

Author	Sex: Age &	Duration (Year)	Squam. Cell.	Basal Cell.	Mixed Sq. & Basal Cell.	Adeno-Carcin.	Unclassified
Wolff H. (22)	21 F	Unknown	+				
Singleton A. O. (16)	46 M	Unknown					+
Nosti R. (14)	50 M	20	+				
Schubert H. (15)	46 M	3	+				
Goldman H. & Kalow I. (7)	56 F	1		+			
Tendler M. J. (17)	55 M	20				+	
Baraldi A. (2)	42 M	Unknown	+				
Vara-Lopez R. (19)	67 F	40	+				
Hall A. & Lee J. G. (8)	42 M	20	+				
Hayden E. P. (9)	19 F	Unknown			+		
Weinstein M. & assoc. (20)	43 M	21	+				
Matt J. G. (11)	18 M	One Month			+		
Weinstein M. & assoc. (21)	51 M	15	+				
Hibner R. &. Cohn R. (10)	55 M	24	+				
Hibner R. & Cohn R. (10)	48 M	39	+				
Conole F. D. (5)	62 M	38	+				
Terry J. L. & assoc. (18)	53 M	26	+				
Boulkalik W. F. & Salwan F. A. (3)	61 M	43	+				
Milch E. & assoc. (13)	68 M	Several Years	+				
Cleveland B. R. & Green W. O. (1,4)	32 M	7	+				
Gasto E. A. & Wilde W. L. (6)	86 M	50	+				
Present report	55 F	20		+			
Total: 23 Cases			16	2	2	1	1

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PATIENT PERSONALITIES

The stolid, stoical, taciturn patient may resent questioning and be slow to reply; you must be painstaking and unhurried if an accurate and informative history is to be obtained.—H. U. Hopkins, M.D., Ed., *Leopold's Principles and Methods of Physical Diagnosis. Third Edition.* 1965, p. 3.

The Significance Of Posttraumatic Epilepsy

A. Earl Walker, M.D.

Introduction

■ It is common knowledge that convulsions may occur some time after a head injury. For this reason any episodic posttraumatic neurological incident arouses the fear that it may be an indication of the falling sickness. Fortunately, most paroxysmal disturbances which befall the head injured person are not of that nature, but stem from vasomotor instability. Many are definitely related to a change from the lying to the sitting or standing position. They are often described as blackouts, fainting or dizziness and last only a few seconds. Rarely do they cause an individual to fall to the floor. Often they develop when the patient gets up for the first time, but occasionally they occur later in the convalescence. They may or may not be associated with headache. Although some epileptic attacks may resemble such spells, the latter's association with changes in posture, and their subsidence in a few weeks usually permits an accurate differential diagnosis.

The characteristics of a genuine epileptic attack are usually so typical that even a lay person has no trouble recognizing its nature. In less than 10 per cent of cases, the manifestations are atypical and bizarre. Spells described as a dizzy episode, a paroxysmal light-headedness, a faintness or a blackout without loss of consciousness or a fall, may be fragments of an epileptic attack. However, their nature must remain conjectural unless the episode at times progresses to a convulsive seizure, or fortuitously occurring while an electroencephalogram is being run, is seen to be associated with focal or generalized discharges. A few cases, in any large series of head injuries, must remain unclassified, be listed as posttraumatic epilepsy suspect, or as borderline attacks. Even in the first few months after a head injury their number is small, later it diminishes almost to a vanishing point as the true nature of the condition becomes apparent.

Factors Related To The Development Of Posttraumatic Epilepsy

Not all individuals who sustain head injuries become epileptic; in fact, only a small percentage of those who suffer even severe damage to the brain will ever have a seizure. A number of reasons for this susceptibility of certain individuals have been proposed. Some relate to the subject (intrinsic) and some to the wounding (extrinsic).

Intrinsic or genetic factors. Both direct epileptic tendencies and indirect propensities such as might be reflected by hereditary nervous or mental disorders have been suggested as playing a role in posttraumatic epilepsy. However, a careful genealogical inquiry has not revealed a statistically significant difference in the incidence of epilepsy in the families of men who did not and who did develop seizures as the result of a head injury.[6] Some predisposing conditions such as a head injury in early childhood or trauma at the time of birth, has been proposed as a factor. It has been suggested that the first-born who is more likely to have trauma in the primiparous pelvic outlet than later children, might be more susceptible to seizures. However, these hypotheses have not been borne out in testing. Nor is there proof that individuals having childhood diseases associated with convulsions are more likely to have posttraumatic epilepsy than children who did not develop seizures. Hence, although an intrinsic factor is suspected, its nature has not been determined.

Extrinsic factors. Unquestionably, many parameters of the head injury influence the probability of seizures developing at some future time. Some of these such as depth of wounding have been well documented, others such as the presence of intracerebral foreign bodies are conjectural, but not proved. These factors may be divided into those relating to the impact, the site of injury and the wound.

The impact. The parameters of impact are related to the physical characteristics of the agent—its mass, shape, density, velocity and its mode of contact. In clinical parlance these factors are inherent in the concepts of missile and non-missile injuries, blunt and penetrating head wounds and so forth. There has developed the idea that there is a basic difference in wounds categorized in this fashion. If such is the case, it would be logical to discuss the sequelae of these different forms of in-

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jury as distinct entities, and not as events along a continuum. Yet these divisions are often arbitrary, and some have vague borderlines between them. The closed head injury with a basal fracture in one classification may be called an open head injury in another.

Because accurate assessment of the physical forces of impact are not obtainable in most cases, the above categorizations are useful in that they indicate general classes or degrees of impact forces which affect the head. In this respect, they give an index of the severity and nature of the stresses to which the brain is subjected.

The wounding. There is general agreement that factors related to the severity of wounding in all its aspects—stresses at impact, vascular reaction including edema, iatrogenic complications, reaction to foreign bodies, infection, healing and so forth—are important determinants of the probability of epilepsy. These factors may be assessed in terms of the physical parameters of anatomical involvement, the degree of physiological impairment, and the rate and amount of anatomical and physiological restitution. In clinical terms, the physical parameters of anatomical involvement include the extent of wounding (scalp, skull, meninges, brain) and the dimensions of the wound. The physiological impairment relates to such clinical phenomena as duration of unconsciousness, period of amnesia and degree of neurological deficit. Restitution includes the factors of healing—cerebral edema, infection, reaction to foreign bodies and blood, type of wound healing, primary or delayed, and so forth. Each of these factors plays a role of varying importance in determining the likelihood of an epilepsy developing. For example, only 15 per cent of patients with large scalp lacerations develop seizures, whereas, 41 per cent of those with brain wounds are so afflicted (Table I).

Location of injury. Another important extrinsic factor relates to the location of the brain wound. Recent experimental work[4] has shown that various parts of the brain are to different degrees capable of epileptogenicity. Motor cortex, hippocampus and amygdala much more readily develop epileptoid activity than the polar regions of the cerebral cortex and the subcortical ganglia. Hence, the part of the brain damaged becomes an important consideration in the likelihood of a posttraumatic epilepsy (Table II).

TABLE I

RELATION OF EPILEPSY TO DEPTH OF WOUND

DEPTH OF WOUND		EPILEPSY (PERCENTAGE)	
	ASCROFT (1) N = 299	CAVENESS (2) N = 356	WALKER & JABLON (11) N = 207
Scalp	24		15
Dura mater	23	19.5	17
Brain	45	50	41

TABLE II

RELATION OF LOCATION OF MISSILE WOUNDS WITH DURAL PENETRATION AND EPILEPSY

REGION	RUSSELL & WHITTY (9)		WALKER & JABLON (11)	
	No.	%	No.	%
Prefrontal	160	39	153	28.8
Frontal	127	55		
Parietal	170	65	213	40.1
Temporal	71	38	79	14.9
Occipital	73	38	86	16.2

Attempts to correlate the chances of a posttraumetic epilepsy with one or two highly sensitive factors have not been wholly successful. Ritchie-Russell and Smith[8] examined a hundred factors and concluded that the severity of brain damage most closely related to duration of unconsciousness and the period of amnesia. In closed head injuries the period of unconsciousness is roughly proportional to the severity of brain damage and the likelihood of epilepsy. But in open head injuries, this factor is not so sensitive for patients with large losses of brain tissue may have had no impairment of consciousness at the time of the injury and yet be subject to a high risk of epilepsy (Table III).

The Type Of Seizure

Almost all varieties of attacks are encountered in posttraumatic epilepsy, although there is a somewhat higher percentage of focal seizures than in the "idiopathic" epilepsies. The focal manifestations, in general, correspond to the functional representation of the damaged brain, but there are discrepancies due to contre-coup and secondary cerebral wounds. Although the convulsions presumably originate in a traumatized cerebral focus, at least one-fourth of posttraumatic epileptics have no conscious warning of their generalized seizure. Motor phenomena such as twitching or jerking of a limb, sometimes associated with paresthesias, are an equally common mode of onset of the seizure. Somewhat less frequent are sensory auras with or without comcomitant or subsequent twitching or jerking. Other manifestations of cerebral dysfunction, such as visual, auditory or psychic disturbances less commonly herald the onset of the attack. The so-called psychomotor attacks are not frequently seen. It is extremely rare, if ever, that true petit mal epilepsy with a 3/sec. spike and dome electroencephalographic pattern occurs as the result of a head injury. Although a few isolated cases have been reported, their validity has been doubted by some authors.

TABLE III
RELATIONSHIP OF PERIOD OF UNCONSCIOUSNESS TO EPILEPSY

	CLOSED HEAD INJURIES AND SCALP LACERATIONS WITHOUT NEUROLOGIC DEFICIT.	OPEN HEAD INJURIES WITH HEMIPARESIS.
No unconsciousness	2/40* = 5.0%	16/26* = 61.5%
Unconsciousness up to two hours	5/53* = 9.4%	12/25* = 48%
Unconsciousness morethan two hours	4/18* = 22.2%	23/35* = 65:6%

* This fraction represents the number of individuals in this category with epilepsy over the total number of individuals in the category.

With the passage of time the type of attack may change, usually from a generalized to a focal seizure or in some cases, the pattern of the seizure alters so that attacks which initially began with one aura may be ushered in by a different warning after a few years (Table IV). A detailed examination of those cases in which the character of the attacks changed suggests that patients with motor, sensory, adversive or other auras had attacks in later years beginning with phenomena usually ascribed to a focus in the temporal lobe, namely gustatory olfactory, epigastric aura. In fact, this type of metamorphosis was present in some 12 of 30 cases having a change in the character of the attack.[12] The electrographic abnormalities in some cases also showed a shift from a frontal to a temporal focus.

The Onset Of The Epilepsy

Seizures may occur after a blow to the head at almost any time. In approximately 1 per cent of individuals sustaining a head injury, a convulsive seizure results from the immediate trauma to the head. These seizures may not be of serious prognostic omen, if other factors of wounding are minor. However, the prognosis is grave for stuporous patients who have generalized seizures some hours after a severe head injury. Focal seizures in the first days are less serious. They are usually considered to be due to cerebral lacerations or blood in the spaces about the brain; in fact, some surgeons consider that their occurrence is an indication for an exploratory burr hole. In the first few weeks after a head injury, focal seizures, presumably due to the acute inflammatory reaction to brain damage, are not uncommon. Their prognostic significance for later seizures is not agreed upon; some authors consider them so benign that they do not classify them as posttraumatic epilepsy. However, about half of these patients will have later attacks.

TABLE IV
RELATIONSHIP OF TYPE TO
CHANGE IN CHARACTER OF SEIZURE
OVER A TEN YEAR PERIOD

	TOTAL	NO CHANGING	PERCENTAGE
Focal attacks only	22	5	22.4
Focal, some becoming generalized	77	13	16.9
Focal, all becoming generalized	48	7	14.6
Generalized only	32	5	15.6
Psychomotor and other	4	0	—

Although few patients with closed head injuries will develop seizures after the first month or two, those with open head wounds have a considerable risk of seizures occurring within the first two years. In the latter group approximately 50 per cent of those who will develop epilepsy have had their first attack by six months after injury, and 80 per cent have had an attack before the end of the second year. Thereafter, patients with closed head injuries who have no attacks are very unlikely to have seizures, but those with open head wounds have about 1 per cent chance each year of developing attacks until the 10th postrtaumatic year (Fig. I). Occasionally a patient may have his first attack 15 or 20 years after a head injury, but such a late onset should lead to a very careful search for other possible causes.

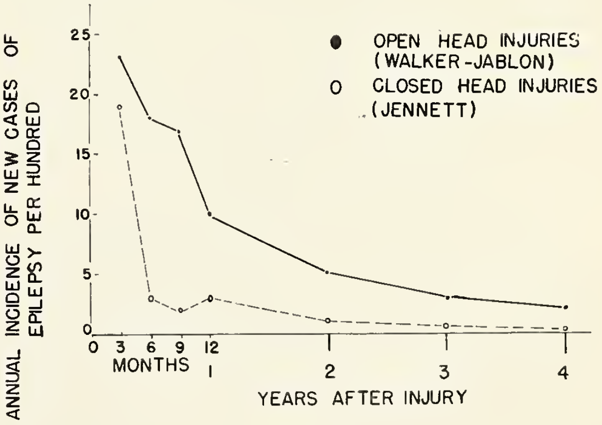

FIGURE I
Graph to show the annual incidence of posttraumatic epilepsy in a series of closed (circles) and open (dots) head injuries.

TABLE V

INCIDENCE OF EPILEPSY IN CLOSED HEAD INJURIES* AND DURAL PENETRATING INJURIES (FROM WALKER (11)

AUTHOR	CLOSED NO. CASES	 % EPILEPSY	OPEN NO. CASES	 % EPILEPSY
World War I				
Rawlings	47	9	226	33
Credner	241	19.7	1,234	49
World War II				
Walker & Jablon	267	14.2	472	36
Wilson			196	17
Civilian				
Rowbotham	430	2.5		
Jennett	1,000	8.0**		
Korean				
Caveness (table II)	149	10	130	50

* Includes scalp lacerations.

** Deduced from 3.8% early epilepsy plus 5% late epilepsy of which ¼ to ⅓ were early epileptics.

The Incidence Of Posttraumatic Epilepsy

The incidence of posttraumatic epilepsy varies with the type, location and severity of head injury (Table V). For closed head injuries, a figure of 1-5 per cent is usually quoted, for open cranial wounds, the figures range from 20-50 per cent. If an attempt is made to control the severity and type of wounding, the incidence of seizures is remarkably similar. For example, the overall incidences of posttraumatic epilepsy in missile head-injured men of World War I,[1] World War II,[11] and of the Korean campaign[2] are practically identical, 33.5 per cent, 33 per cent and 34 per cent respectively. This finding has been advanced as evidence that surgical advances did not affect the frequency of convulsive sequelae. But the optimist might well ague that the improved surgical treatment saved the more seriously wounded men of the later wars, many of whom unquestionably would have succumbed had they been similarly wounded in World War I, so that had the true incidence and other factors including surgical treatment been the same, there would have been a higher percentage of posttraumatic epilepsy in the later wars.

Course Of The Posttraumatic Epilepsy

Sufficient information is now available from the long-term followup of relatively large series of patients to describe the natural history of posttraumatic epilepsy. It becomes apparent that some individuals following a head injury, will have a few convulsions in the first year or so and no subsequent attacks, even though anticonvulsive medication is not maintained. Patients with generalized attacks without aura are a little more apt to have this benign course than individuals with focal seizures that become generalized. However, in this latter group, there is a tendency for the attack to remain focal without spread. Hence, in a series of posttraumatic epileptic patients, the prevalence of major attacks decreases more rapidly than that of minor attacks. In addition, the focal attacks become less severe and decrease in frequency so that an occasional paresthesia of a hand may be the only remaining fragment of the focal seizure (Fig. II).

Yet, it must be admitted that occasionally an individual who has been free of attacks for 5 or 6 years may have a seizure often precipitated by an intercurrent infection, traumatic or psychic stress and/or the sudden withdrawal of anticonvulsive medications. In general, these attacks are isolated and upon returning to a normal regime, the patient continues indefinitely without further attacks.

In a series of 230 patients who had had one or more seizures after a head injury and who were followed for 15 years, approximately one-fourth had no attacks of any type from the 5th to the 15th years and almost half had no major convulsions in that period. In other words, 10 to 15 years after injury, 60 per cent of these posttraumatic epileptics no longer have attacks which render them incapable of taking care of themselves. A number of factors point toward a favorable prognosis. The occurrence of only generalized and few attacks within the first month or so of injury, and a tendency for the attacks to decrease in frequency or severity in the first two years, are good prognostic omen. Anticonvulsant medication may be a

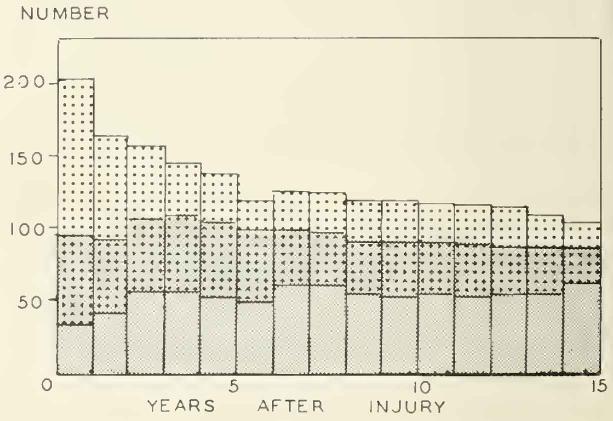

FIGURE II

Graph to show the prevalence of posttraumatic epilepsy in a series of 230 men known to have had one or more seizures following a head injury. The clear areas represent no seizures. The coarse dotted areas represent major attacks and the stippled areas represent minor attacks without loss of consciousness. Note that the number of men having minor attacks remains constant because of the number of men ceasing to have minor attacks is balanced by the number of men whose attacks change from major to minor. After the fifth year the attack profile is relatively stable.

Table VI
Electroencephalographic Findings as an Index of Prognosis of Posttraumatic Epilepsy
(from Marshall & Walker)

EEG characteristics 5-9 Yrs. after onset of posttraumatic epilepsy	State of Epilepsy after 5 Yrs. No attacks No. cases	%	Cont'd attacks No. cases	%
Normal or borderline	27	39	56	34
Generalized abnormality	17	25	32	23
Focal abnormality	25	36	55	33

factor, but it is not essential, for many patients whose attacks ceased are not taking drugs.

The Value Of Electroencephalography In Posttraumatic Epilepsy

High hopes have been entertained for the electroencephalogram to provide prognostic information regarding head injuries. Single records are difficult to evaluate because the pretraumatic electroencephalographic pattern is unknown. Serial tracings may give significant information regarding the extent and degree of brain damage, but they do not indicate which patients will eventually develop postraumatic epilepsy and which will not, nor do they indicate the prognosis of an individual having seizures (Table VI). It is now apparent that no specific electroencephalographic pattern is consistently associated with posttraumatic epilepsy. Even spikes generally considered to have epileptic significance are not much more frequent in the records of patients with posttraumatic epilepsies than those of non-epileptic patients with head injuries. Serial records do not enable an accurate prognosis, for although episodic discharges may precede convulsions, they may also resolve without overt seizures.

On the negative side a normal electroencephalogram after a head injury is indicative of little or no brain damage; an abnormal tracing is usually associated with some brain injury. A series of brain waves showing gradual recession of abnormalities over a period of months is looked upon as a satisfactory resolution of the injury, whereas, the persistence of abnormalities is a cause of apprehension. Perhaps the use of activating techniques will allow more definite conclusions to be drawn regarding the future probabilities of epilepsy.

If a convulsive state has developed, the electroencephalogram still seems to be more sensitive to the degree of brain damage than to the epileptic state. Within the first ten years of injury, electroencephalograms of patients who had had one or more seizures, of patients who were having recurrent seizures and of those who had not had a convulsion for at least two years, did not specifically differ in terms of wave, form, frequency or synchrony (Table VI), but with a longer span of freedom — ten years — the brains of the non-epileptic group tended to be less abnormal than those of the other groups (Table VII).

The Treatment Of Posttraumatic Epilepsy

Theoretically the administration of anticonvulsant medications should decrease the likelihood of an epilepsy developing. However, no well-controlled series has yet been presented to prove this hypothesis. Because all anticonvulsant drugs occasionally have undesirable side-effects, it does not seem advisable to prescribe such medication indiscriminantly for patients who have had minor head injuries, and who consequently have very minimal chances of developing seizures. On the other hand, patients with severe open wounds of the head, who have a 50 per cent chance of developing a seizure, may well be advised to take an anticonvulsant drug for one or two years after their injury. If no attacks have occurred by this time, the odds are slight that they will develop later. The effectiveness of anticonvulsant medication in posttraumatic seizures has been questioned by some epileptologists. However, in my experience the attacks are easier to control by anticonvulsive medication, than those of other forms of epilepsy. Phenobarbital in doses of 0.1 grams, t.i.d. or dilantin in doses of 0.1 gram q.i.d. is advisable for a patient who has had one or more attacks following a head injury. If they persist, the medication should be increased and mysoline added. Rarely is it necessary to consider surgical exploration of the wound and resection of an epileptogenic focus.

The Disability From Posttraumatic Epilepsy

A few convulsive attacks after a head injury should not be considered a permanent disability, even if they are associated with some neurological handicaps such as a hemiparesis or aphasia. Almost

Table VII
Relationship of Electroencephalographic Findings at Followup to State of Epilepsy

	Type of Abnormality None (N = 33) %	Generalized (N = 29) %	Focal (N = 50) %
Minor Attacks			
None 10 yrs.	61	55	52
1–6/yr.	9	14	18
6+/yr.	30	31	30
Major Attacks			
None 10 yrs.	82	63	56
1–6/yr.	12	20	34
6+/yr.	6	17	10

TABLE VIII
RELATIONSHIP OF WORK STATUS AND INTELLIGENCE

INTELLIGENCE	EMPLOYED (N = 96) No.	EMPLOYED (N = 96) %	NON-EMPLOYED (N = 117) No.	NON-EMPLOYED (N = 117) %
–89	11	11	65	55
90–109	53	55	46	40
110+	32	34	6	5

all authors agree that the presence of a posttraumatic epilepsy rarely constitutes a real handicap to social or economic rehabilitation. However, the patient will have a few anxious years, but he should not become depressed nor give up his occupation because of such attacks. A rather extensive experience indicates that if the individual has better than a normal intelligence, the odds are about 7 out of 8 that he will be able to continue his normal occupation. Even motoring, after a short interlude, is not denied him. Unfortunately, individuals with low intelligence do not make as satisfactory adjustments to their handicap as those with normal or superior intelligence (Table VIII).

Summary

The factors influencing the development of a posttraumatic epilepsy are many and related to events preceding, concomitant with and subsequent to the injury.

The incidence of epilepsy following head injuries varies from practically nil to over 50 per cent depending upon the severity of injury and the site of cerebral involvement.

Even if seizures develop, spontaneous regression and cessation may occur 3-4 years after the injury.

The medical treatment consists of anticonvulsant therapy until the patient has become free of attacks for at least two years.

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WILLIAM HEBERDEN 1710-1801

It may be noted that among his colleagues and friends were John and William Hunter, Fothergill, Jenner, Sir George Baker, Withering, Pitcairn and Robert Gooch, men who in point of time followed Heberden, and bridged the road to the development of the great group headed by Richard Bright.—Prefatory Essay, by Leroy Crummer, William Heberden. *An Introduction to the Study of Physic.* New York, Paul B. Hoeber, Inc., 1929, p. 17.

Infected Subdural Hematoma

David M. Geetter, M.D. and Stevenson Flanigan, M.D.

■ Reports of suppuration within the intracranial subdural space have appeared in the medical literature for several centuries as documented in the articles by Webster and Gurdjian,[1] and Groff and Grant.[2] Beginning with the paper by Virchow[3] in 1857 in which he presented the histological description and pathological study of subdural fluid collections, a great volume of literature has been written concerning the nature of intracranial effusions and infections of the subdural space. The subject is usually confined to three basic categories –subdural hygroma, subdural hematoma, and subdural empyema, with very little mention of coexistence between any two of these conditions. Recent cases of a seldom encountered entity, suppuration within a pre-existing subdural hematoma, prompted a review of the literature on the phenomenon. Although this entity has been previously recognized and has been reported in papers on subdural empyema (Hankinson and Amados,[4] Hitchcock and Andreadis,[5] List,[6] Lancet[7]) as a coincidental finding, no reference dealing specifically with this condition was encountered. The rarity of infection occurring in a subdural hematoma may be appreciated by the fact that in a large collection such as McKissock's, et al.[8] series of 387, Munro's[9] series of 310, and Laudig's et al[10] series of 143 cases of verified subdural hematomas, no mention is made of secondary infection. Similarly, in a review of 98 cases of subdural hematoma in children by Ingraham and Matson,[11] no infections were encountered. Surprisingly, in review articles on infections of the subdural space by Gurdjian and Webster,[12] Kubik and Adams,[13] Stern ad Boldrey,[14] Botterell and Drake,[15] Keith,[16] and Spatz,[17] pre-existing subdural hematoma is not listed as a concommitant factor. Although infected subdural hematomas have undoubtedly been recognized, and no pretense is made of proposing a new clinical entity, it is intended to establish the infected subdural hematoma as a distinct suppurative lieson apart from subdural empyema. Three representative case histories recently encountered on the Neurosurgical Service at the Yale-New Haven Hospital will be presented.

Case No. 1

R.H. This was a nine month old Negro male who had sustained a head injury with fracture of the left parietal bone at age six months. Apart from a generalized seizure immediately after the injury, there were no neurological sequellae and studies including an EEG were normal. In the succeeding three months he developed a progressive right hemiparesis beginning in the lower extremity. Two weeks prior to admission he was treated with penicillin for a draining right otitis media. No culture of the drainage was taken. On re-admission the child was febrile and difficult to arouse. There was bilateral otitis media. The neck was stiff and he exhibited a spastic, hyperreflexic hemipareses of the right extremities, and right facial weakness. The head circumference had increased from 44 cm. to 48.5 cm. in the three months. Fundiscopic examinations were normal. Lumbar puncture revealed 60 W.B.C. predominantly polymorphonuclear leukocytes. Cultures of the CSF were sterile. The proteon was 128 mg per cent, CSF sugar, 59 mg. per cent (blood, 96 mg. per cent). Antibiotic therapy was re-instituted and the child was operated upon on an emergency basis because of progressive deterioration. Bilateral parietal burr holes were made. The dura was thickened on the left and a thick gray membrane was encountered beneath it. On opening the underlying membrane an odorless, yellow-white seropurulent fluid spurted out. Gram stain of the fluid revealed numerous inflammatory cells but no organisms. Cultures of the fluid were sterile. The cavity was drained. Rapid return of right sided function occurred post-operatively and there was no evidence of re-accumulation. An EEG at the time of discharge revealed a preponderance of slow activity in the left temporal area.

Case No. 2

L.McC. This was a 72 year old white female with a history of a slight left sided weakness since 25 years of age, and focal left sided motor seizures once or twice monthly in the recent ten years. There was no history of significant head trauma. Three days prior to admission she developed right fronto-temporal headache and had several generalized seizures. The frequency of the left sided motor seizures also increased to at least 30 per day and she rapidly developed a complete left hemiplegia. On admission she was lethargic and febrile without discernible cause of the fever. There was a dense, flaccid left hemiplegia and a suggestion of a homonymous left temporal visual field cut. A Babinski sign was present on the left. Skull films were normal but the pineal was not visualized. An echoencephalogram showed a 1.5 millimeter shift of the midline structures from right to

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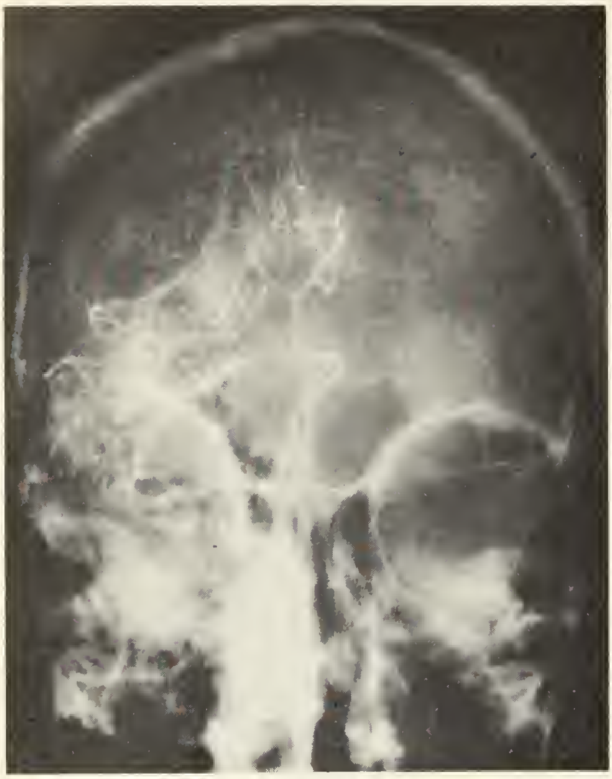

FIGURE I

Case 2. Right carotid arteriogram showing the localized subdural collection indicating chronicity of the process.

left. An Hg^{203} brain scan demonstrated an increased uptake in the right parietal area. Lumbar puncture revealed an opening pressure of 170 mm. water. There were 113 cells, predominantly lymphocytes. The CSF protein was 164 mg. per cent; sugar 113 mg. per cent (blood sugar 225 mg .per cent). Cultures revealed no growth. Subsequent spinal taps showed persistent elevation of protein and slightly elevated cell counts. The initial EEG recorded a diffuse abnormality with suppression of voltage over the right hemisphere. On several EEG studies, a preponderance of high voltage slow activity was appreciated in the right frontal area. She continued to run a low grade temperature for the next four weeks despite intensive antibiotic therapy. Suspecting the possibility of a brain abscess, carotid angiography was performed. It showed a large right fronto-parietal subdural collection, the convex appearance of which suggested chronicity (Fig. 1). A right parietal burr hole revealed thickened dura. Beneath the dura was a firm gray membrane measuring three millimeters in thickness. On incising this membrane a two millimeter thick layer of softer yellow-white membranous material was encountered. Biopsies of both layers were taken. Upon puncturing the inner material, a large quantity of thick yellow-white odorless fluid escaped. It filled a cavity measuring three centimeters in depth, 12 cm. anterior, four centimeters posterior, and five centimeters inferior to the burr hole. The cavity was lined on all surfaces by an amorphous yellow material and had numerous loculations of the fluid. A stained smear of the fluid revealed chronic inflammatory cells but no organisms. All cultures were sterile. Histological sections of the biopsied membranes showed the outer membrane to be a fibrous tissue with hemosiderin deposits and large thick-walled vascular channels consistent with a subdural hematoma membrane. The inner membrane contained dense fibrous but more cellular tissue with small areas of necrosis and several thick-walled vascular channels. Post-operatively the left hemiplegia cleared rapidly and her seizures ceased. She was kept on anticonvulsant therapy.

Case No. 3

R.K. This was a 56 year old white male who had sustained severe head, left arm and spinal cord injuries in an industrial accident in 1952. No intracranial surgery was performed and on discharge a year later there was no evidence of cerebral dysfunction despite palsies in his lower extremities and left arm. He was readmitted in March, 1963, for treatment of decubiti of the sacrum and both hips, infected with Staphylococcus aureus. Ultimately, it was necessary to remove the head, neck and proximal portions of the femurs bilaterally. During his hospitalization he was disoriented and showed evidence of generalized mental deterioration without signs of focal intracranial disorders. He remained febrile and his wounds drained material which consistently grew out Staphylococcus aureus, although blood cultures were sterile. On September 4, 1963, he developed a right facial weakness, slurred speech and a dilated, fixed right pupil. Edema of the right eyelid was noted. He began to have generalized seizures and a progressive loss in level of consciousness. Echoencephalogram revealed a 1.5 centimeter shift of the midline structures to the left. On September 6, 1963, a right parietal burr hole revealed a two millimeter thick membrane beneath the dura. Incision of the membrane yielded a large subdural hematoma which contained a few clumps of yellow material in the drainage. Cultures of the subdural fluid grew Staphlococcus aureus and an enterococcus. Death ensued on September 14th. Autopsy revealed a large subdural abscess over the convexity of the right parietal lobe (Fig. 2). Histological section of the dura demonstrated a subdural

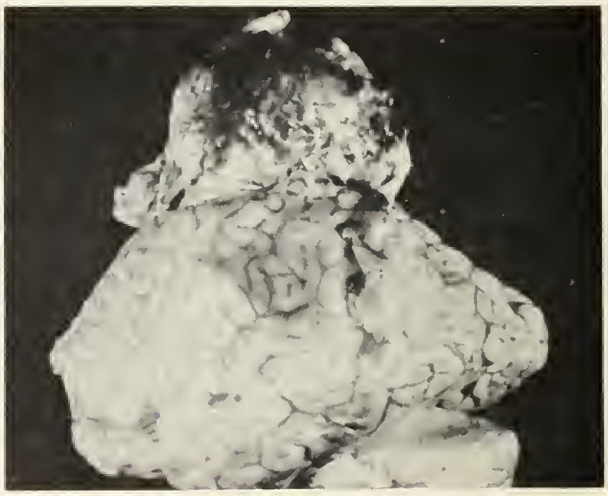

FIGURE II

Case 3. Brain removed at autopsy. The dura and the suppurative subdural hematoma have been elevated superiorly to show the depression and discoloration of the adjacent brain surface.

membrane typical of that found in chronic subdural hematoma with associated acute inflammatory cells. Another finding was an abscess in the left kidney with acute and chronic pyelonephritis.

Discussion

In each of the cases evidence of a pre-existing subdural hematoma is apparent. The child developed a slowly progressive hemiplegia several weeks following head trauma having exhibited no neurological abnormalities at the time of the original injury. A thick subdural membrane was encountered at the time of surgery, typical of that found in chronic subdural hematoma. In the second case, despite the lack of known antecedent skull trauma, the patient's history of left sided weakness and seizures, the angiographic picture, together with the histological findings of the membranes biopsied at surgery, indicate the presence of a long standing subdural hematoma. The third case is one of a more acute nature but again, a subdural membrane was found with watery red-amber fluid in the subdural space at the time of surgery.

As is most often seen, these subdural collections were confined to the convexity of the cerebrum. The "basal" subdural space is rarely involved in accumulations of this sort because of the intimate relation of the irregular base of the brain with the fossae of the skull and its attachments to the cranial base by means of the cranial nerves (Courville and Blomquist).[18] On the dorso-lateral surface of the brain and in the interhemispheric fissure where bridging veins are commonplace there is less interruption of the space and large collections may accumulate. The mesothelial cells lining the subdural cavity then participate in the encapsulation of these extraneous materials by proliferation and vascularization.

The dura itself is generally resistant to penetration by adjacent infection although extension into the subdural space may occur by contiguity with a purulent process. More commonly, the route of infection is retrograde via venous or perivascular pathways, and metastatic via the blood stream from distant sources. Stern and Boldrey[14] list ten etiological conditions for the access of organisms into the subdural space. The most common source is otorhinological disease (Schiller, et al,[19] Courville),[20] but even here the blood-borne metastasis is frequently the source of contamination. Only the first case presented falls into this category; Case #2 had no recognized source of infection; and Case #3 belonged to the group with infection metastatic from a distant source. The use of antibiotic therapy prior to surgery accounts for the sterility of the fluid in the first two cases, and the resistant nature of the organism in Case #3 provided a positive culture of the subdural collection. The "granulation" tissue comprising the pre-existing subdural membrane might serve as a nidus for infection in filtering organisms from the blood stream in bacteremia. The chronicity of the membranes would likely limit the infection to that area circumscribed by these membranes. No evidence of pus was apparent outside the confines of the hematoma cavities.

Diagnosis of this condition as distinct from subdural empyema, subdural hematoma or brain abscess may be difficult. Shift of the pineal or midline structures on echoencephalogram, pleocytosis of spinal fluid, focal neurological signs and abnormalities on brain scan, EEG, or contrast studies may be similar in all of these conditions. A history of antecedent trauma with intervening neurological signs in a patient who develops fever and exacerbation of the neurological abnormalities can logically raise the question of an infected subdural hematoma. The finding of a subdural collection on contrast studies in a febrile patient with no other explanation for the fever may support the suspicion. Otorhinologic, scalp or distant systemic infections in patients with previous head trauma should alert one to the possible development of an infected subdural hematoma, especially if fever continues unexplained after successful eradication of the primary infection. The rarity of this condition makes it probable that few will be diagnosed preoperatively.

The treatment of an infected subdural hematoma is logically that of any collection of "laudable pus" in the body—drainage. Results in these cases were gratifying with simple "burr hole" trephination, irrigation, breaking loculations, instillation of antibiotic solutions and drainage with Penrose drains. The fluids from two was already sterile so that in essence the surgical management was simply that of evacuating a space-occupying lesion. In the third, with a still infected hematoma, the surgical intervention did not alter the course, but then the patient was also suffering pyelonephritis, kidney and lung abscesses, and was in a debilitated state. No attempt was made to remove the membranes or make further drainage. Systemic antibiotic therapy was continued.

The neurological status of all three patients was markedly improved after the procedure. Follow-up examinations on the two surviving patients four months after surgery revealed continuing neurological improvement and no evidence of re-accumulation of the subdural collection. In the light of the generally poor prognosis in patients with subdural suppurations, the rewards of early recognition of the infected subdural hematoma with its simple treatment and favorable prognosis are self evident.

Summary

1. There are scant reports in the literature of infected subdural hematomas as a suppurative lesion distinct from subdural abscess or empyema.

2. Three cases of infected subdural hematoma with their salient clinical and histopathological features are presented.

3. Reference is made to factors determining sites of subdural accumulations. The formation of the subdural membrane and the potential role it plays in the localization of infection is discussed.

4. The diagnosis of infected subdural hematoma may be difficult to make pre-operatively. A history of antecedent head trauma in a patient with unexplained fever, neurological signs and a subdural collection on contrast studies may suggest the diagnosis.

5. Treatment has been effective with drainage of the subdural cavity and systemic antibiotic therapy. The prognosis is favorable.

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PATIENT PERSONALITIES

To avoid leading questions, which too often receive an affirmative reply whether correct or not, it is sometimes useful to reword the question in an opposite manner and repeat it later. For example, if you desire to know whether walking or other physical exercise produces pain in the chest, you might say: "Does walking help your pain?" If the patient replies emphatically, "That's when I get it," his answer is probably reliable.—H. U. Hopkins, M.D., Ed., *Leopold's Principles and Methods of Physical Diagnosis. Third Edition.* 1965, p. 3.

THE PRESIDENT'S PAGE

OLD WORDS — NEW MEANINGS

THAT communication should become increasingly complex and difficult is undoubtedly a natural consequence of specialization. For the medical profession some areas of confusion are based perhaps more on concepts and approaches compartmentalized within limited fields of interest than on differences in vocabulary. However when discussions involve interdisciplinary groups, the difficulty is often magnified because the participants "speak a different language". This has been notable particularly in the effort to bring advances in engineering to usefulness in medicine. Progress toward a fusion of bio-engineering knowledge has been delayed largely for that reason.

Evidence of even widespread difficulty exists. Many who converse with members of the New Generation find communication impeded not only by the unfamiliar sounds included in their vocabulary but also by the widely differing connotations of many use-aged words such as "cool" or "cat"—or even "freedom", "rights" and "morality". Some elders, particularly those who deal with the practical problem of decision-making and translation of concepts into reality, feel keenly an urgency to establish better rapport and a common ground of understanding with youth. A persistent language-barrier could provide the basis for harsh criticism of judgment, or misguidance by our leaders, when the "go-go camp" reaches its period of responsibility and performance.

The problems of communication are not limited to this facet of society. Although the implications are less esoteric, it has become apparent to those concerned with current considerations of legislation for implementing Title XIX (Medicaid) in Connecticut that confusion exists in respect to the meaning of certain key-words which appear in the bills. There is need for clear understanding and uniformity of interpretation by physicians, legislators, administrators, intermediary agencies, and others. An attempt has been made by the Committee on Insurance and Prepayment Plans of the AMA Council on Medical Services to aid in clarifying procedural terminology by the development of a booklet for distribution to members. Since this effort is necessarily dynamic in nature, continuous addition and revision (frustration has been encountered in the attempt to obtain nation-wide uniform interpretation of some words) will be required. Definition of terms which are very important to an understanding of Title XIX such as: poverty, welfare, charity, indigent and medically indigent, categorical needy and medical needy, are lacking. These terms do, however, merit much thought and review in relation to modern socio-economic concepts.

No attempt will be made here to provide a lexicon of even those words found in the bill which may be of common use but may have multiple or vague meanings. In view of the questions asked by members of the Society and in the interest of common parlance and mutual understanding at least in Connecticut, it is felt useful to outline the following definitions of terms related to charges and reimbursement of physicians for medical service:

(1) The word "usual" means the fee that a physician charges most of his private patients for a given service. In the terminology used by some other organizations, our word "usual" is synonymous with their word "customary".

(2) To us, the word "customary" means that the usual fees of a physician are in line with the levels generally accepted as proper in his community area for a similar service rendered by a practitioner of similar qualifications. In the parlance of others, the word "prevailing" may be used as a synonym for "customary".

(3) The phrase "as determined at local level" is intended to apply to both (1) and (2) in the sense that the propriety of a physician's fee should *not* be measured against some fixed, uniform, state-wide schedule or standard, but should be evaluated in terms of what is deemed reasonable and proper in his own community or area. For practical administrative purposes, the Society looks upon its eight component county medical associations as best qualified to make such "local level" evaluations, and each one of them has a review committee in-being to receive and pass judgment on any member's fee which is questioned by a third party payor (insurance company, Welfare Department, etc.).

ORVAN W. HESS, M.D.

FROM THE GENERAL MANAGER'S OFFICE

William R. Richards, m.d., *General Manager*
160 St. Ronan Street, New Haven, Conn.
Telephone 865 0587

Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

SUMMARY OF ACTIONS COUNCIL MEETING

Wednesday, December 21, 1966

I. Attendance

In the absence of the Chairman, Stevens J. Martin, President Orvan W. Hess chaired this meeting. Present in addition to Dr. Hess were: Drs. Bradley, Gardner, M. Caplan, Polivy, Rogol, Grendon, Abbot, Hastings, Ayres, Nolan, Cramer, Fabro, Grant, Petrie, Pelz and Roch. Also present were: Mrs. Lindquist, Mr. Villano and Dr. Richards.

Absent were: Drs. W. Martin, Goldberg, Brandon, H. Caplan, Weise, Sr., S. Martin, Egan, Spitz, Shepard, Ciccarelli, Wilson and Palomba.

II. Routine Business

Approval Of Minutes

As printed and distributed, it was VOTED to approve the minutes of the meeting of December 8, 1966.

Life Membership

It was VOTED to approve applications for Life Membership received from the following eligible Active Members of the Society:

Timothy F. Brewer, Sr., West Hartford, (HCMA) 1967
David W. Byrne, Windsor Locks (HCMA) 1967
Ettore F. Carniglia, Windsor Locks (HCMA) 1967
Francis L. DePasquale, Hartford (HCMA) 1967
Asa J. Dion, Hartford (HCMA) 1967
Francis X. Fagan, West Hartford (HCMA) 1967
Clarence M. Friery, West Hartford (HMCA) 1967
Manuel S. Hirshberg, Hartford (HCMA) 1967
Joseph Kalett, New Britain (HCMA) 1967
Milton F. Little, Hartford (HCMA) 1967
Morris M. Mancoll, Hartford (HCMA) 1967
Rudolph Maslak, Warehouse Point (HCMA) 1967
Joseph T. Matteis, New Britain (HSMA) 1967
Ladislaus B. Slysz, New Britain (HCMA) 1967
Reuben E. Thalberg, Southington (HMCA) 1967
N. Weisenfeld, Hartford (HCMA) 1967

Student Members

It was VOTED to elect to Student Membership two Connecticut residents who are attending medical schools as follows:

David J. Beccia, East Ridge Drive, Middlebury
New York Medical College—Class of 1970
Pre-Med: Fordham University
Parent: Martin J. Beccia

Winthrop S. MacLaughlin, Jr., 46 Ledge Lane, Stamford
George Washington Univ. Sch. of Med—Class of 1970
Pre-Med: Fordham University College of Pharmacy
Parent: Deceased

Resignations, Appointments, Etc.

Alternate AMA Delegate: It was VOTED to appoint Sidney L. Cramer, Hartford, as Alternate Delegate to the AMA for the term Jan. 1, 1967-Dec. 31, 1968, replacing Morris P. Pitock, Bridgeport, deceased. As Alternate Delegate, Dr. Cramer will be paired with Delegate Max Caplan, Meriden, and his appointment will be recommended for confirmation to the next meeting of the CSMS House of Delegates.

Committee on Public Health: It was VOTED to accept the resignation of Gert M. K. Wallach, Torrington, as a member of this Committee, and to appoint Fowler White, Torrington, to replace Dr. Wallach on the Committee as the LCMA representative for the current year.

Delegate to Maine Medical Association: It was VOTED to accept, with regret, the resignation of Clyde L. Deming, New Haven, as a CSMS Delegate to the Maine Medical Association, and to refer the question of appointing Dr. Deming's successor to the Committee on Preliminary Study of Nominations for 1967-68.

Conference Committee with Connecticut Bar Association: It was VOTED to accept, with regret, the resignation of Peter V. C. Dingman, Waterbury, as a member of this Conference Committee, and to thank Dr. Dingman for his many years of service, as a member, and as chairman, of the Committee.

Date Of Next Meeting

Wednesday, January 11, 1967, was set as the date of the next meeting.

III. Old, New And Special Business

Appointment Of Delegates To The New England Council

As revised at its November, 1966 meeting, the bylaws of the Council of the New England State Medical Societies now call for the appointment of *six* Delegates from each constituent medical society instead of the former *three*. At the request of the CNESMS, six CSMS Delegates were appointed for the balance of the current year as follows:

M. David Deren, Bridgeport (incumbent)
Ralph L. Gilman, Storrs (incumbent)
Orvan W. Hess, New Haven (new, by virtue of office as President)
E. Tremain Bradley, Norwalk (new, by virtue of office as President-Elect)
Max Caplan, Meriden (new)
Gaert S. Gudernatch, Sharon (new)

Oliver L. Stringfield, incumbent Delegate, remains a member of the N.E. Council ex-officio, as a Past President of that organization, and is now *not* included as a regular Delegate from CSMS.

Report—Committee On Third Party Payments

It was VOTED to accept as information a report filed by the Committee on Third Party Payments which covered the following matters:

(a) *Urging Insurance Carriers to Issue Supplementary Coverage to Medicare B*: Having determined that numerous carriers are making such coverage available to Connecticut residents age 65 years and older, the Committee feels the Society does not need to take action in this regard. The matter was received from the HCMA Board of Directors and was referred to the Committee for study and report.

(b) *Disclaimer re Acceptance of Assigned Benefits:* The Committee approves of the idea of attaching a "disclaimer" to all claims in which assignment of benefits are accepted, such disclaimer to state that the benefits accepted are not to be interpreted by anyone as necessarily being related in any way to the physician's usual and customary fee. The Committee recommends that the wording of the disclaimer be worked out by the General Manager, in consultation with CSMS legal counsel, and then submitted to the Council for final approval and possible distribution to the Society's members for their use.

(c) *Louisiana State Medical Society's Direct Billing (IRP) Program*: The Committee approves of the "philosophy and procedure" of the LSMS program of direct billing to all patients but feels (1) that we should await the possibility of incorporating procedures similar to those of LSMS as a consequence of legislative changes being made in the Title XIX program of Medical Assistance to permit direct billing of MA recipients, and (2) that the General Manager should seek to determine how such IRP plans are working in the several (about 12) states in which they are being tried out.

Report—Special Committee On Title XIX Legislation

It was VOTED to accept the report filed by the Special Committee on the legislative goals to be sought by the Society at the next General Assembly with respect to the implementation of Title XIX program of Medical Assistance in Connecticut, with the following specific exceptions:

(a) It was VOTED to inform the Society's legislative agent that, in preparing a bill to authorize the payment of "usual and customary fees" to physicians rendering care to Title XIX beneficiaries, he should insert a clause to cover the phrase "as determined at local level" (*without* using that phrase) which would stipulate that, under the auspcies of CSMS, review committees of the eight component county medical associations would be available to the Welfare Department to advise whether a questioned fee was "usual and customary" in the community area in which the service was rendered. This action was felt to be necessary to clarify the term "usual and customary fees, *as determined at local level*" and to place it in full context with the Society's policy in this matter, which policy *includes* a review committee mechanism at local (county medical association) level to receive and rule upon questions regarding the propriety of local (county area) physicians' charges.

(b) The Council was in agreement with the report's recommendation that the Society *not* introduce a bill regarding specific income levels to be set for MA eligibility by the General Assembly. In keeping with the resolution on this subject adopted by the House of Delegates (December 8), however, the members did not agree that the Society should plan to remain silent about income levels. It was therefore VOTED to prepare a "position paper" dealing with the philosophic and socio-economic aspects of setting income standards beyond "humanitarian and fiscally prudent" levels with respect to the definitions of indigency and medical indigency in Connecticut, and to give the "position paper" the widest possible distribution among members of the General Assembly. Further, at the proper time and at the proper hearing, the Society should be prepared to present testimony on this question which will be based on said position paper.

(c) It was VOTED to direct the staff to explore the possibility of holding a second Conference of County Medical Association Officers in conjunction with a statewide symposium on the implementation of a Title XIX program of Medical Assistance in Connecticut. Held under the auspices of the Society, such a symposium could be planned in such a way as to afford medical leaders and members of the General Assembly an opportunity to become oriented on the *medical aspects* of Title XIX and to allow *all* participants to exchange views and ask questions on same. The plan to be prepared by the staff is to include such details as: date, place, costs, format, etc.

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When she's experiencing acute discomfort from cold symptoms, it's small wonder the patient becomes distressed about her condition.

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Novahistine LP is a long-acting decongestant that helps restore normal mucus secretion and ciliary activity—physiologic mechanisms which prevent infection of the respiratory tract. A dose of two tablets taken in the morning and repeated in the evening will usually keep air passages clear for 24 hours.

Use cautiously in individuals with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution patients who operate machinery or motor vehicles that drowsiness may result.

Each Novahistine LP tablet contains: phenylephrine hydrochloride, 25 mg., and chlorpheniramine maleate, 4 mg.

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NOVAHISTINE® LP

For relief of nasal congestion.

Request—Connecticut Pharmaceutical Association

Pursuant to an earlier request for CSMS cooperation in "legalizing" the prescribing of Class A narcotics by telephone, the Executive Committee of the CPA asked for the Society's support of a bill (to be introduced at the next General Assembly) permitting physicians to prescribe, and pharmacists to dispense, Class A narcotics via the telephone. It was VOTED to inform the Executive Committee of the CPA that the Council endorses the principle of the CPA's legislative objective in this matter, and will be pleased to receive a copy of the bill to be introduced for study and possible support. In taking this action, many members of the Council expressed the opinion that "adequate safeguards" against opening any doors to illicit traffic in narcotics should be embodied in such a bill.

Agreement With Office Of Dependents' Medical Care Program

The Council received a December 6 letter from ODMC stating that, due to a misunderstanding, no specific progress has been made by ODMC toward accommodating the Society's policies on "usual and customary fees" in the basic three-party agreement between the Society, ODMC and CMS, Inc. (as fiscal intermediary); that, however, ODMC was willing to try to draw up such an agreement along the lines sought by the Society and to meet with CSMS representatives for this purpose. It was VOTED to notify ODMC that, based on this declaration of intent, the Society would sign the supplemental agreements covering outpatient care and care of retired military personnel and their dependents (new coverage), such supplemental agreements to continue in effect until March 31, 1967 the date on which the extension of the present basic agreement terminates; and, further, that the Council will be disposed to renew all agreements with ODMC, effective April 1, 1967, provided that (a) provision is made for paying physicians on the basis of "usual and customary fees", without reference in the agreements to any fixed schedule of payments; that (b) the CSMS Relative Value Schedule is used by ODMC as a guide to relating the time-skill-knowledge values of all covered services; and that (c) questions concerning usual and customary fees will be referred to county medical association review committees for study and opinion.

Definition Of Term "Medically Necessary" Re Utilization Of Physicians' Services

As official definition of the term "medically necessary" as applied to the utilization of physicians' services, it was VOTED to adopt the following:

It Is Moved: That the Council of the Connecticut State Medical Society adopt as official CSMS policy the following definition of the term "medically necessary" as it may be applied to the utilization of physicians' services:

For the Physician: Any professionally recognized medical service that is prescribed and/or rendered by a licensed physician, which is in reasonable accord with the customary standards of medical practice obtaining in his community area, should ordinarily be accepted without question as being "medically necessary" by the patient and/or third party payors. When the medical necessity of such a service is questioned by the patient and/or a third party payor, the question should be referred promptly for review and opinion to the county medical association of which the physician is a member.

For the Patient: Any professionally recognized medical service that is prescribed and/or rendered in good faith by a licensed physician at the request of a patient consulting him should ordinarily be accepted without question as being "medically necessary" by third party payors. When the medical necessity of the patient's request is questioned by a third party payor, such question should be resolved exclusively by the patient and the third party payor.
and it is further

Moved: That the Council notify all recognized third party payors operating in Connecticut of this policy, and request their cooperation in implementing its purpose.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on December 21, 1966. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT WANTED

OBS-GYN—Board eligible, 31 years old, seeks association leading to partnership. Will complete military obligations February 28, 1967. Had 4 year residency, fully trained.

RADIOLOGIST — Board eligible, Connecticut license. Would like to do locum tenens for months of January and February.

PLACEMENT OPPORTUNITIES

PSYCHIATRIST—full-time for small, but expanding psychiatric inpatient service in general hospital. Short-term therapy provided on open ward. Also, Mental Hygiene Clinic and Day Treatment Center on hospital grounds which offer continuity of care. There will be opportunities for

controls infected inflammatory dermatoses that start from scratch

Neo-Synalar®
(fluocinolone acetonide-neomycin sulfate cream)
Cream

The "itch-scratch" cycle usually associated with inflammation often results in infected dermatoses because broken skin surfaces are particularly vulnerable to pathogenic bacteria.[1] To treat infected inflammatory dermatoses, Neo-Synalar Cream combines the most active topical corticosteroid with a highly reliable antibiotic generally reserved for topical application.

In Neo-Synalar, fluocinoline acetonide controls the inflammation and provides rapid relief from associated pruritus. At the same time, its antibacterial component — neomycin — combats superficial infection caused by many gram-positive and gram-negative bacilli[2] that often colonize and thrive on abraded skin.[1]

A specially formulated vanishing cream base that is greaseless and odor free makes Neo-Synalar cosmetically appealing, and encourages greater patient cooperation.

controls the infection

stops the scratch

Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of its components. **Precautions:** Neomycin rarely produces allergic reactions. Prolonged use of any antibiotic may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy should be instituted. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. **Side Effects:** Side effects are not ordinarily encountered with topical corticosteroids. As with all drugs, however, a few patients may react unfavorably to Neo-Synalar under certain conditions. **Availability:** Neo-Synalar Cream (0.025% fluocinolone acetonide, neomycin sulfate, equivalent to 0.35% neomycin base), 5 and 15 Gm. tubes.

References: 1. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: A manual of cutaneous medicine, Philadelphia, Saunders, 1961, p. 79. **2.** Barber, M., and Garrod, L. P.: Antibiotic and chemotherapy, Baltimore, Williams and Wilkins, 1963, p. 111.

teaching paramedical personnel and inservice programs. Salary dependent upon qualifications. Excellent fringe benefits. Apply: Chief of Staff, VA Hospital, Newington, Connecticut 06111.

PEDIATRICIAN—Large multi-specialty group is looking for fourth man for the Department of Pediatrics in a large city in Connecticut.

SENIOR PHYSICIAN—Physician with training in internal medicine needed as ward physician in a general medical ward in fully accredited State Veterans general medical and surgical hospital. Excellent fringe benefits, including furnished house or apartment and maintenance, when available, at low cost. Salary range: $13,040-$17,040. Contact: E.O. Buetsch, Personnel Officer, Veterans Home and Hospital, Rocky Hill, Connecticut.

HOUSE PHYSICIAN—Diversified duties in 135-bed accredited voluntary hospital. Connecticut license required. Monday through Friday and every other Saturday morning. Salary: $15,000 yearly plus 3-room furnished apartment. Contact: Administrator, Park City Hospital, Bridgeport, Connecticut 06604. Telephone: Area Code 203:368-0201.

RADIOLOGIST—350-bed general hospital needs third radiologist for general diagnostic work. Isotopes, therapy and special procedures available, if interested. A new 9-room department is being built. Starting salary: $25,000 with yearly increments. Contact: Howard F. Root, Jr., M.D., c/o Department of Radiology, New Britain General Hospital, New Britain, Connecticut 06050.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

1967 MEETINGS

March 30—183rd Annual Meeting of New Haven County Medical Association will be held at Waverly Inn, Cheshire, Connecticut, at 3:30 p.m.

April 12-13—Seminar on Hospital Infections in Connecticut jointly sponsored by Connecticut State Medical Society, Connecticut Hospital Association, Yale Medical School, Connecticut State Department of Health and the Communicable Disease Center of the Public Health Service at Valle's Steak House, Hartford, Connecticut.

April 25-27—175th Annual Meeting of the Connecticut State Medical Society to be held at the Hartford-Hilton Hotel, Hartford.

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ARTISTS, ATTENTION

The Connecticut Physicians Art Association is planning the 1967 Art Exhibit in conjunction with the Annual Meeting of the Connecticut State Medical Society. This will be held at the Statler-Hilton Hotel, Hartford, Connecticut on April 25, 26, 27, 1967.

All previous exhibitors are invited to show their works at this meeting and new exhibitors among physicians and their families are cordially invited to join the group of art hobbyists. Works eligible will include oil, water color, tempora, black and white, etchings, photography, pastels, sculpture and ceramics. Eligible exhibitors are members of the Connecticut State Medical Society, their wives and children. Art works will be judged in four categories: 1. children through 16 years (over 16 will be judged with adults); 2. beginners to three years; 3. over three years; 4. professional.

A hanging fee of one dollar ($1.00) will be charged for each entry and fifty cents ($.50) for children under 16 with three pictures allowed per artist. Pictures should be framed and wired for hanging. The exhibition will be judged by professional artists.

Entry blanks will be mailed to former exhibitors and may be obtained by writing to the below address. A special effort will be made to recognize merit in each group so it is important to fill in the entry blank completely, stating the number of years you have been enjoying this hobby. Professional artists are welcome and will be judged in the professional class.

Art works must be submitted to a representative of the Art Association in the lobby of the Statler-Hilton Hotel on Sunday, April 23rd between the hours of 12 and 3 P.M. Parking temporarily near the side entrance is possible for the few minutes involved in dropping off these art works. Please forward entry blanks and checks to the address below prior to April 15th. Make checks payable to Connecticut Physicians Art Association.

If further information is needed, the following persons may be contacted for information:

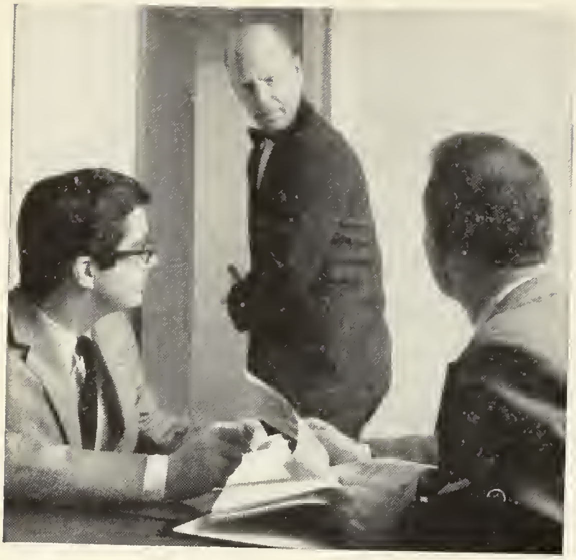
Stewart J. Petrie, M.D., President, 56 Minerva St., Derby, Conn.
Mrs. Orvan Hess, Vice President, 29 Old Orchard Rd., North Haven
Edward Williams, M.D., 269 Church St., Naugatuck
Charles O'Neil, M.D., 18 Asylum Street, Hartford
Herman Austrian, M.D., 935 White Plains Rd., Trumbull

Other auxiliary members that may be contacted if further information is needed include:

Hartford County:	Mrs. Ernest Rosenthal, 17 Pine Street, West Hartford Mrs. Merrill Rubenow, 68 Butternut Road, Manchester Mrs. David Waskowicz, 35 Whitemen Road, New Britain
Middlesex County:	Mrs. Clarence Harwood, 1350 Old Mill Road, Middletown
Windham County:	Mrs. Ralph Gilman, Willow Brook Road, Storrs Mrs. William S. Maurer, Babcock Hill Rd., South Windham
New Haven County:	Mrs. Mark Hayes, 163 Ridgewood Avenue, North Haven John Hoffer, M.D. 153 Main Street, Ansonia
New London County:	Mrs. Albert Gosselin, R.F.D. #4, Norwich Mrs. Roland A Mariani, 99 Ocean Avenue, New London

Since a good Art Show will add much to the success of this annual meeting, participation and cooperation of all art hobbyists is solicited.

Stewart J. Petrie, M.D., *President*
Connecticut Physicians Art Association



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...consolidates fluid stools with pectin
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Each fluid ounce of creamy white suspension contains:
Paregoric (equivalent).........(1.0 dram) 3.7 ml.
Contains opium (¼ grain) 15 mg. per fluid ounce.
warning: may be habit forming
Pectin .... (2½ grains) 162 mg.
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Usual Adult Dose: One or two tablespoonfuls three times daily.

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- **effective neutralizing power**—Two tablets in vitro[1], provide nearly 2 hours' relief within effective pH range 3 to 5.5.
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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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Around The State

Connecticut Nutrition Council

The Connecticut Nutrition Council, in conjunction with the Advisory Nutrition Committees to the Public Health Committee of the Connecticut State Medical Society and the Connecticut State Dental Association held a meeting at the LaScala Restaurant, Berlin Turnpike, on January 18, 1967 at 6:30 P.M.

The guest speakers were Dr. John W. Patterson, Dean of the School of Medicine and Dr. Lewis Fox, Dean of the School of Dental Medicine, University of Connecticut. They spoke on the development of the two new schools.

Dr. Patterson has an unusually broad background of experience and accomplishment in research, teaching and administration. A graduate of Ohio Wesleyan University in 1939, Dr. Patterson received a Master's degree in 1941 and a Ph.D. in organic chemistry in 1942 from Ohio State University. He entered Western Reserve University School of Medicine and obtained his M.D. degree in 1949. Following graduation he remained at Western Reserve as Assistant Professor and then as Associate Professor of Anatomy. Active in the various planning groups, he became the first Coordinator of the new basic science program and subsequently the first Associate Dean of Medical Education, responsible for the entire undergraduate medical curriculum.

In 1956 Dr. Patterson left Cleveland to become Professor of Anatomy and Dean of the new School of Medicine at the University of British Columbia, where he remained for two years. From 1958 through 1963 he served as Dean of Medicine, Director of Medical Affairs, Vice-Chancellor for Medical Affairs, and Professor of Physiology at Vanderbilt University. In 1963 Dr. Lyman Stowe, then Dean of The University of Connecticut School of Medicine, prevailed upon him to join the planning group at The University of Connecticut as Professor of Physiology. Following Dr. Stowe's untimely death, Dr. Patterson was appointed Acting Dean and later to his present position as Dean of the School of Medicine.

Dr. Lewis Fox, Dean of the School of Dental Medicine, as a member of the planning staff, has had the longest association with the developing Health Center. He was also a member of the Site Selection Commission which chose the Farmington location for the Health Center.

Dr. Fox graduated from the University of Maryland School of Dentistry in 1927. While in private practice in South Norwalk, Connecticut, he became nationally recognized for his pioneering work in the field of periodontics. He has co-authored several text books on periodontics and periodontal therapy and is widely known as a lecturer and teacher.

At the time of his appointment as Dean of the School of Dental Medicine, Dr. Fox was Professor of Periodontology at the Boston University School of Medicine, Associate Professor of Periodontology in the Graduate School of Medicine of the University of Pennsylvania, and Associate Clinical Professor of Dentistry in the School of Dental and Oral Surgery of Columbia University. He is a Diplomate of the American Board of Periodontology and a member of the American College of Dentists. For the past three years he has served on the National Advisory Dental Research Council, the body which acts on dental research grant applications and determines program policy for the Dental Research Institute of the National Institutes of Health, U.S. Public Health Service.

In addition to a number of other honors, Dr. Fox recently received the Fones Award of the Connecticut State Dental Association and the Waterbury Dental Society award for outstanding contributions to dentistry.

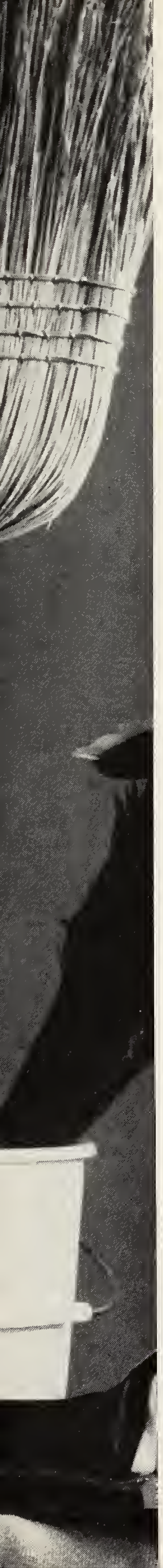
You—The Red Cross—And Servicemen

Your services as a physician or medical authority may be called upon frequently by the American Red Cross in connection with its Congressional responsibility to provide voluntary relief and service programs to members of our armed forces and their families.

The execution of these services is the joint effort of 3600 local chapters linked through a rapid communications network with Red Cross Field Directors serving military personnel around the world.

When servicemen and women are separated from their families, problems often accompany the separation and military authorities, as well as families at home, rely on the Red Cross to obtain and transmit verified information when certain decisions must be made.

Your assistance in providing vital professional information may come about in any of the following situations:



Posed by professional model.

You can't set her free. But you can help her feel less anxious.

You know this woman.

She's anxious, tense, irritable. She's felt this way for months.

Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough.

SERAX (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability, thus strengthening her ability to cope with day-to-day problems. Eventually—as she regains confidence and composure—your counsel may be all the support she needs.

> Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.
>
> May be used in a broad range of patients, generally with considerable dosage flexibility.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

Precautions: Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed upon cessation questionable withdrawal symptoms. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

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1. You may be contacted by Red Cross personnel to verify the need for military authorities to grant emergency leave for a serviceman because of serious illness in his family. In some cases, you may even want to initiate such a request yourself on behalf of a patient.

2. A member of the armed forces, his family, or the Red Cross, may also request a written statement from you, supporting a serviceman's application for transfer or even discharge from duty, due to the serious illness of a family member.

2a. If you believe the request to be valid, a report on your letterhead should include the nature, onset and duration of your patient's illness, the nature of care required, the degree of temporary or permanent disability, any possible future developments and professional recommendations.

All medical statements prepared for the military should include an exact diagnosis, prognosis and the anticipated life expectancy of the patient.

The information given to Red Cross and military authorities is confidential if you request that it not be shared with the serviceman concerned.

Priority for rapid transportation of a serviceman overseas returning to this country will be influenced by the nature of your report.

The Red Cross will also notify a serviceman, either overseas or on board ships at sea, about the birth of his child. Such messages should include the sex, weight and time of birth as well as the physical condition of both mother and child.

The Red Cross will also, either at the request of a physician or the family, notify a serviceman about the death of next of kin. Information desired is the cause and time of death.

Professional medical information relayed through the Red Cross communications system can be of great value to members of the armed forces in assuring them of the opportunity to deal with family situations as they would want to if they were at home.

From Yale University School Of Medicine

The United States Public Health Service has awarded a grant of $239,000 to the Yale School of Medicine to study the design and organization of a community health program with prepaid services provided through group practice.

The study, which is being conducted by Professor Isidore Sydney Falk, will also consider the feasibility of establishing such a program in conjunction with a teaching medical center.

Announcement of the study was made by Dr. Vernon W. Lippard, Dean of the medical school.

Mr. Falk, who is Professor of Public Health for Medical Care in Yale's Department of Epidemiology and Public Health, is a recognized authority in the field of medical care planning. He was among the authors of the original Social Security program in 1935 and served for many years in Washington in the development of the social security system and national health legislation.

The present study directed by Professor Falk will extend over a period of two to three years. It visualizes the possibility of establishing a health center through which a limited group of families would have the privilege of obtaining comprehensive health care on a voluntary basis, including preventive health services and medical care for the sick in the health center, hospital, at home, or elsewhere. Financing would be arranged through prepayment.

It is expected that the program, including the health center, would be operated by a community non-profit corporation, and would be staffed by a medical care team organized to furnish comprehensive care, including family physicians and specialists, nurses, social workers, and technicians. Patients would be hospitalized at local hospitals.

The study is exploring three possible developments regarded as very important by the U.S. Public Health Service: first, how a community health plan can have the greatest benefit from the special medical skills available in a large medical center; second, how the provision of the health services can be made most effective without sacrifice of quality; and third, how the health center can be made available for the training of young doctors to participate in comprehensive care furnished in a group practice setting.

If the local labor unions should establish such a program, consulting services of the Yale medical faculty would be available at the request of the health center staff, just as they are available to other referring physicians throughout Connecticut, Dean Lippard pointed out. He emphasized, however, that neither the Yale School of Medicine nor the Yale-New Haven Hospital would assume direct responsibility for the program. "Our primary concern is that if such a program is established in New Haven, it should be of the highest quality," he said.

Working on the study with Professor Falk are Dr. Gordon K. MacLeod, Assistant Clinical Professor of Medicine at Yale; Marvin M. Leeds, associate in health center administration, and a number of consultants.

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OBITUARIES

William B. Smith, M.D.

1893 - 1966

Dr. William B. Smith of Wethersfield, former Surgeon General of the State of Connecticut, died at the Hartford Hospital on October 15th, 1966, after a long illness. He was 73 years of age.

Born in Phillipsburg, N.J., he was a graduate of Bethlehem Preparatory School, Lehigh University, University of Pennsylvania School of Medicine, and the United States Army School of Aviation Medicine. In 1929 and 1947 he continued post graduate studies in Nose and Throat Surgery and Dermatology at the University of Pennsylvania Graduate School of Medicine.

Dr. Smith served in both World War I and World War II. In World War I, he served with Base Hospital No. 10, University of Pennsylvania Hospital Unit attached to the British Army in Belgium. While in the service he won the Army Commendation Medal and the Army Commendation Ribbon.

A military man for some 30 years, Dr. Smith was promoted to Brigadier General upon his retirement from the Connecticut National Guard in 1953. He was former Commanding Officer of the 118th Medical Detachment, Connecticut National Guard; was Medical Officer for the State Staff of the Connecticut National Guard and was flight Surgeon for the 43rd Division, Aviation. Dr. Smith devised a medical survey system which was adopted all over the nation.

His civilian medical positions included, Chief Medical Officer of the Connecticut State Prison, courtesy staff of the Hartford Hospital and consultant at Rocky Hill Veterans Hospital.

Other positions he held were, Secretary and Treasurer of the Aero-Medical Division, a national organization of medical men interested in flight medicine; and Assistant Medical Director of Connecticut Mutual Life Insurance Co., and Connecticut General Life Insurance Company.

He was a member of the American College of Preventive Medicine; The Hartford, County and State Medical Societies; Bourne-Keeney Post-23, American Legion; Hospitality Lodge 128 AF & AM; The Wethersfield Cove Yacht Club; the Charter Oak Council of Boy Scouts and the First Church of Christ Congregational, Wethersfield. He was also a founder of the Sea Scout Ship No. 66 of Wethersfield, and was an Honorary Member of the 1st Company, Governor's Foot Guard.

Dr. Smith was a man of protean interests and activities. He was a source of inspiration and guidance and materially assisted many young physicians in their salad days. Dr. Smith served God, his country and his practice well. He was a beloved, conscientious physician, who will be sorely missed by his host of friends, his multitude of grateful patients and by his family.

John T. Winters, M.D.

J. Harold Root, M.D.

1893 - 1966

Dr. James Harold Root died suddenly on December, 3, 1966, at home of coronary occlusion, at the age of 73.

Dr. Root was born April 1, 1893, son of the late Samuel and Mary Elizabeth (Stone) Root.

He graduated from Taft School 1911. Sheffield Scientific School, Yale 1914, Harvard Medical School 1918. He completed his formal training at Boston City Hospital and at the Harriet Lane Home. He served with the U. S. Army Medical Corps in World War I.

In 1920 Dr. Root returned to Waterbury where he enjoyed a large practice in pediatrics until his death. He was a member of the Waterbury Hospital Staff for 46 years and served as President for the Staff 1934 to 1935, as Chief of Pediatrics from 1948 to 1953, as Chief of Staff from 1953 to 1954. He was associated with the Waterbury V.N.A. for 22 years. He played the most important part in establishing Well Baby Stations in Waterbury. In 1938 he was President of the Waterbury Medical Society and was Treasurer thereof from 1942 to 1948. He was President of the New Haven County Medical Society in 1940.

Dr. Root was a charter member of the Hezekiah Beardsley Pediatric Club and served as president in 1937-38.

Dr. Root served the Connecticut State Medical Society as a member of the House of Delegates, member of the Committee on Public Health since 1936 and its Sub Committee on School Health since 1952. He organized and chaired the Committee on Nutrition in 1958. The Connecticut Advisory Committee on School Health owes its inception to Dr. Root. Since 1936 he was a member of the State Advisory Committee on Maternal and Child Health Services. He also served on the Advisory Committee to the State Commissioners of Welfare, Finance and Control. He represented the Connecticut State Medical Society on the State Planning Group for the Mid-Century White House Conference on Children and Youth in planning for the White House Conference of 1960.

Dr. Root assisted in writing the original "School Health Policies" in 1939. He was a Fellow of the American Academy of Pediatrics and was Chairman of the Connecticut Chapter of the Academy from 1943 to 1948 during which time he supervised the Academy Study of Child Health Services in Connecticut.

Dr. Root participated unstintingly in the Pediatric aspect of his community and State and leaves an enveiable record of accomplishment in his field. His good judgement, willingness to work, quiet efficiency as well as his unfailing good humor filled his life with good deeds and endeared him to all who knew him.

Joseph L. Hetzel, M.D.

In Memoriam

Giuffirda, Francis — Meriden, Tufts Medical School, 1937. Dr. Giuffirda was a general practitioner and surgeon in Meriden in 20 years. During World War II he served in the Navy as a Captain and received the Bronze Star Award for his service. Dr. Giuffirda was a member of the Meriden-Wallingford Medical Society, the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. He was a diplomate of the American Board of Surgery and a fellow of the American College of Surgeons. Fox six years, he was director of surgery at the Meriden Hospital and attending surgeon at the Bradley Memorial Hospital and at the World War II Veterans Memorial Hospital. He was a member of many civic associations, including the United Fund and the Red Cross. Dr. Giuffirda died December 17, at the age of 56.

Miller, Robert M.—New Milford, Columbia College of Physicians and Surgeons, 1926. Dr. Miller was former chief of staff at the New Milford Hospital and had practiced in New Milford for 16 years. He was a member of the Waramaug Medical Society, the Litchfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Miller died December 28, at the age of 68.

Doctor's Office

Frank J. Riccio, M.D. announces the association of Vincent J. Scavo, M.D., for the practice of otolaryngology and maxillofacial surgery at 823 East Main Street, Bridgeport.

Walter T. Shanley, M.D. announces the opening of an office for the practice of orthopedic surgery at 2660 Main Street, Bridgeport.

James K. Yue, M.D. announces the opening of an office for the practice of internal medicine at 725 South Main Street, Middletown.

NEW BOOKS IN REVIEW

THE CELL: An Atlas of Fine Structure: Its Organelles and Inclusions. Don W. Fawcett, M.D. 448 pages. 240 figures. Wm. B. Saunders Company, Philadelphia and London 1966.

Reviewed by: LOUIS H. NAHUM

The electron microscope and its ancillary methods have now opened up the cell for visual exploration and have extended our knowledge of the structural organization of protoplasm down to the level of macromolecules. As a result there has grown a convergence of the sciences of cytology, biological chemistry and cell physiology.

In this book is a collection of electron-micrographs illustrating in a beautiful and instructive manner the biological ultra-structure of the cell. The volume actually contains the original electron-micrographs used in the course on general histology and cytology at Harvard Medical School. It is an excellent laboratory manual that can be used in courses in all biology in college and in histology and cytology in Medical schools. It does show a reasonably well integrated picture of the form, topographical relations and functional significance of the principal fine structural components of the cell, the organelles, cell inclusions, and cell surface.

The organelles shown are the nucleus, centriole, mitochondria, Golgi complex, endoplasmic reticulum, ribosomes, lysosomes, microbodies, microtubules and filaments in the muscle cell.

The cell surface is presented by an extraordinary collection of pictures: The cell membrane, external coats, specializations of the surface for cell to cell attachments, myelin sheaths of nerves, transient differentiation associated with surface activity, pseudopodia in phagocytosis, surface folds in pinocytosis, vesicles. Then there are the stable differentiation such as microvilli motile cell processes, flagella, and sperm tails.

What shines out in these pages is that there is a much more complex arrangement in cells than we ever dreamed of. The way the various cells in the body behave becomes clearer to us. It is not surprising that there is developing a new orientation in physiology and biochemistry towards an interest in simpler levels of organization. As our knowledge of them grows, however, we will begin to put the pieces back again and ultimately we will be looking again at organs, systems and organisms with a better understanding of how and why things work to maintain the integrity of the living organism.

SYNOPSIS OF NEUROLOGY, 2nd Edition. Price $7.50, 218 pages. Francis M. Forster. C. V. Moseby Company, 1966.

Reviewed by: LOUIS H. NAHUM

This book is in two parts. The first is devoted to the evaluation of the neurologic potential of a patient and deals with taking a history, doing a physical examination and the various clinical diagnostic tests. Part 2 is devoted to clinical neurologic entities including also disease of muscle.

The methodologies used in making an evaluation of a neurologic patient consist of visual fields, caloric testing, audiometric testing, cystometrography, electroencephalography, electromyography, roentgenography, contrast roentgenography, radioistotope scanning, myelography, cerebrospinal fluid studies and distinguishing between subarachnoid hemorrhage and a traumatic lumbar tap.

Even so it is not a neurologists neurology but it is excellent for the medical student beginning his clinical work and as a refresher to any physician who is not expecting to become a neurologist. Its value has extended beyond the doctor into the paramedical field and should find particular usefulness among nurses and social workers. It is refreshing that eponyms have been reduced to a minimum and when used are included as parenthetical names.

SURGERY OF THE PAROTID GLAND by Robin Anderson, M.D., F.A.C.S. and Louis T. Byars, M.D., F.A.C.S., C. V. Mosby Co., 1965. 177 pp. with 196 illustrations. $12.75.

Reviewed by: MAX TAFFEL

The parotid gland shares with the thyroid the distinction of being close to a critical motor nerve which, if injured, may lead to disastrous consequences. Surgery of the parotid gland is conditioned to a large extent, if not entirely, by the intimate proximity of the facial nerve with the gland. If it were not for this anatomical relationship of the facial nerve, practically all the controversies relating to the surgical management of diseases of the parotid gland would be readily and amicably resolved.

After presenting a brief historical, embryological and anatomical background, the authors describe in some detail all the major neoplastic, inflammatory and traumatic conditions with which the gland is afflicted. The discussions are concise and lucid, and are presented with the authority and assurance that come from an intimate familiarity with the subject.

The authors take their stand on debatable issues with firmness and without equivocation, even though the preponderance of surgical opinion may be against them. When they mention contrary views, they do so only to dismiss them.

In respect to identification of the facial nerve at the time of operation, a step considered to be imperative by most surgeons, the authors have this to say: "Just how often this trunk of the nerve need be identified is questionable. Some surgeons insist that it should be found as the primary effort in every procedure on the parotid gland. With this concept we disagree, primarily because such identification is not necessary. Furthermore since isolation in the presence of tumor inflammation, or severe bleeding may be most difficult, the risk of injury to the nerve under these circumstances is significant. There is no sound reason why the nerve trunk must be found unless a total parotidectomy for benign disease is planned or unless nerve branches must be identified and traced distally, as might be necessary following traumatic division of a branch." (p. 10)

On the issue of multicentricity of benign mixed tumors, they write: "Presumably in an effort to explain a high recurrence rate following their removal it has been stated frequently that mixed tumors are multicentric in origin. There is little or no evidence to support this view. We have personally never seen two mixed tumors in the same gland even if there has been no previous surgery. The only possible conclusion is that multicentricity must be rare, and the appearance of a second tumor following surgery for a primary one can be ascribed only to implantation during the first procedure." (p. 23)

Concerning needle biopsy, there are the following strong words: "There are those who support vigorously the use of transcutaneous needle biopsy of the parotid gland. We do not employ this procedure, and believe not only that it is generally not useful but also that in most instances it is to be condemned." (p. 56)

On the use of the electric stimulator we are told: "The electric stimulator remains a fallible device which requires constant calibration if it is to perform properly. This means not only checking of the instrument to be certain that its wires are intact, its battery is charged, and it is putting out the proper impulse, but also adjusting this impulse for the facial nerve of the specific patient whose response threshold may be very different from that of the previous patient. Like most tools, it is valuable in the hands of an expert; the surgeon inexperienced in its use would do well to use it sparingly and thoughtfully." (p. 123)

On local excision of a benign tumor as opposed to complete resection of the superficial lobe of the parotid, we read: "The object of any procedure for the removal of a benign tumor is to remove the tumor in its entirety, without removing unnecessarily any useful or vital structures. For practical purposes, we attempt to do our tumor excision with a margin of normal parotid gland tissue outside the tumor capsule itself. We do not consider removal of the entire superficial portion of the gland, a procedure commonly known as lobectomy, to have any validity. Those who employ and defend this type of operation do so mainly on the ground that benign mixed tumors of the parotid gland may be multicentric. Their evidence for this idea lies primarily in the high recurrence rate reported by many surgeons for this tumor. . . . Another reason for doing a so-called lobectomy is that it presumably assures a larger margin of normal tissue than an operation in which the tumor is approached directly and removed within the substance of the gland. Unfortunately, this argument does not take into account the fact that the facial nerve and the tumor are virtually always in close contact, there being rarely as much as one millimeter of soft tissue between them. It is not difficult to remove tumor with a satisfactory margin of normal parenchyma anywhere except where the tumor and facial nerve are closely associated. The carrying out of a lobectomy certainly does not modify in any way this particular area of intimacy. If the concept of wide removal is to be valid, then the nerve must also be removed along with a layer of additional uninvolved tissue of the deep portion of the gland." (p. 119)

Finally, to justify their unorthodox position, they say: "The burden of proof in this problem of how to approach a parotid tumor is apparently upon us, since we are the advocates of the conservative operation. In this day of radicality the conservative surgeon finds himself on the defensive. We repeat as our evidence only the pair of statistics that in our experience with more than 350 primary benign mixed tumors which we have removed surgically we have not had any permanent facial palsy and we have only a single patient with a known recurrence in the group. It should be noted that this series consists of only those tumors in which we did the first operative manipulation. Tumors previously biopsied by any route are not included." (p. 128) On the basis of these results, it is hard indeed to quarrel with the authors even though the preponderance of present surgical opinion on many of these issues is squarely against them.

This handsomely printed and profusely illustrated monograft is not and does not claim to be a scholarly and definitive work on the disturbances of the parotid gland. It is rather a recital of the concepts and opinions of two outstanding surgeons who have obviously had a large and varied clinical experience with this subject. It is more in the nature of a practical manual, written in any easy and almost in a conversational style, and providing a few hours of pleasant informative and challenging reading. "Our intent is to discuss parotid gland surgery from a single point of view. We are not trying to outline and review the accumulated data of others nor are we making any effort to be unbiased in our approach. Our conclusions are based on the observation and treatment of more than 600 patients with parotid gland disease over a period of twenty-five years."

SYNOPSIS OF OBSTETRICS, Seventh Edition, by Charles E. McLennan, M.D. Publishers: The C. V. Mosby Company, Saint Louis 1966. 458 pages, $6.85.

Reviewed by: ORVAN HESS

This 458 compendium is the seventh edition of a synoptic treatise on obstetrics with an aim to provide the hurried, or casually interested, student or practitioner with quick and presumably acceptable answers to clinical, or other, problems. The author states that synopses notably are short-lived. For this reason he has added new items and deleted others.

OPERABLE HEART DISEASE; Pathophysiology, Diagnosis, and Treatment. By Howard D. Sirak, M.D. C. V. Mosby Co., Saint Louis, 1966, 130 pp., $12.50.

Reviewed by: HERBERT LEVINE, M.D.

This monograph of 130 pages is presented as a guide to students and house officers rather than as an exhaustive compendium. The first third is devoted to general considerations, and the second and third to congenital and to acquired heart diseases.

The section on general considerations comprises seven chapters two to twelve pages in length, devoted to such areas as routine radiology, special procedures, foetal circulatory physiology, pulmonary hypertension, physiology of total cardiopulmonary by-pass, and problems of pre- and post-operative management. These subjects are dealt with in brief and general terms, and no attempt is made to describe techniques in any detail. The chapter on pre- and post-operative management represents the author's views and methods, and is concise and specific. However, this entire complex field is covered in only twelve pages of text, and a number of problems are not mentioned. The physician who sees these patients in their home communities needs information about later complications such as intravascular hemolysis, and topics such as these are not covered.

The second section discusses nine congenital lesions from the standpoints of anatomy, physiology, clinical findings, special diagnostic procedures, and surgery. Each of these chapters again consists of four to nine pages, some of which are taken up with anatomical charts and reproductions of roentgenograms. The material is clearly presented, but in no great detail. The actual surgery is generally described in a paragraph or two that indicates the nature of the operation.

The section on acquired heart disease is restricted to the four major valvular lesions of rehumatic heart disease, discussed under similar headings. There is no discussion of the entire subjects of pacemakers or surgical approaches to coronary disease.

The book is admirably produced, with an attractive two-color cover, clear type, and a number of excellent diagrams and roentgenographic reproductions. However, it is a brief, though expensive, introductory guide to an extremely complex subject, and as such will probably prove most useful to students and house officers.

CONDITION CRITICAL: OUR HOSPITAL CRISIS by Edwin P. Hoyt. Holt, Rinehart and Winston, New York, Chicago, San Francisco 1966, 241 pp. $5.95.

Reviewed by: ALBERT W. SNOKE, M.D.

Medicine, hospitals, nursing home and extended care facilities, dollars, government, ethics, administrative organization, personnel and the public have all become caught up in a potpourri of interest and emotion that currently is personified in Medicare.

Edwin Hoyt, in his most recent book "Condition Critical: Our Hospital," has approached the whole problem of hospitals and their necessary interrelations with the variety of associated forces affecting institutions in a factual manner that is sympathetic yet critically realistic.

This book is written for public consumption and is obviously not a scientific treatise on any of the chapter headings of "The Voluntary Hospital," "Governmental Hospitals," "Hospitals for Profit," "The Nurse," "Labor," "Special Services," et cetera. However, it is clear that Mr. Hoyt has done his homework seriously and well. He has consulted many individuals in the hospital and medical world and has reflected an unusual depth of thought on this complex subject.

Mr. Hoyt approaches the totality of medical and hospital care from the point of view of the patient, and he has emphasized that our hospital and medical care system is not the best of all possible worlds. He documents his case and ends with the hope that health and hospital administrators, hospital boards of trustees and practicing physicians will recognize this fact.

This book should be of value to all these individuals, for it provides a stimulus to the understanding of the need of a cooperative working relationship between these disparate forces. This would appear to be important if our voluntary system of health care is to continue and to thrive.

BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Human Development by 29 Authorities Edited by Frank Falkner, M.D., M.R.C.P., W. B. Saunders Company, Philadelphia and London, 1966, 644 pp. Illustrated $20.00.

Condition Critical: Our Hospital Crisis. Edited by Edwin P. Hoyt, Holt, Rinehart and Winston, New York, Chicago, San Francisco, 1966. 241 pp. $5.95.

Appraisal Of Current Concepts In Anesthesiology. Edited by John Adriani, M.D., The C. V. Mosby Company, St. Louis, 1966, Vol. 3, 502 pp. $10.85.

Obstetrics And Gynecology. Edited by J. Robert Willson, M.D., Clayton T. Beecham, M.D. and Elsie Reid Carrington, M.D., The C. V. Mosby Company, St. Louis. 1966, Third edition, 727 pp. $15.50.

Gray's Anatomy. Edited by Charles M. Goss, M.D., Lea & Febiger, Philadelphia, 1966, Twenty-eight edition, 1182 illustrations, 1464 pp. $22.50.

Touch, Heart and Pain. Ciba Foundation Symposium. Edited by A. V. S. de Reuck, M.Sc., D.I.C., A.R.C.S., and Julie Knight, B.A., Little, Brown and Company, Boston, 1966, 124 Illustrations, 389 pp. $14.00.

The Thymus. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol., and Ruth Porter, M.R.C.P., Little, Brown and Company, Boston, 1966, 96 Illustrations, 538 pp. $15.00.

Egg Implantation. Ciba Foundation Study Group No. 23, Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A., Little, Brown and Company, Boston, 1966, 25 illustrations, 112 pp.

Histones, Their Role in the Transfer of Genetic Information, Ciba Foundation Study Group No. 24, Edited by A. V. S. de Reuck, M.Sc., D.I.C., A.R.C.S. and Julie Knight ,B.A., Little, Brown and Company, Boston, 1966, 26 illustrations, 115 pp.

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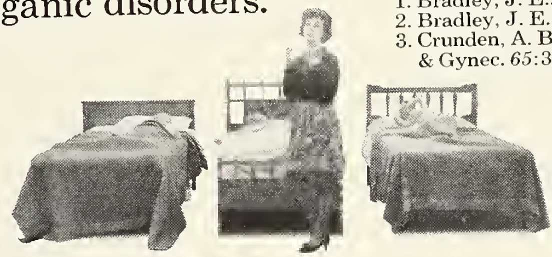
1. Bradley, J. E., *et al.*: J. Pediat. *38*:41 (Jan.) 1951.
2. Bradley, J. E.: Mod. Med. *20*:71 (Oct. 15) 1952.
3. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.



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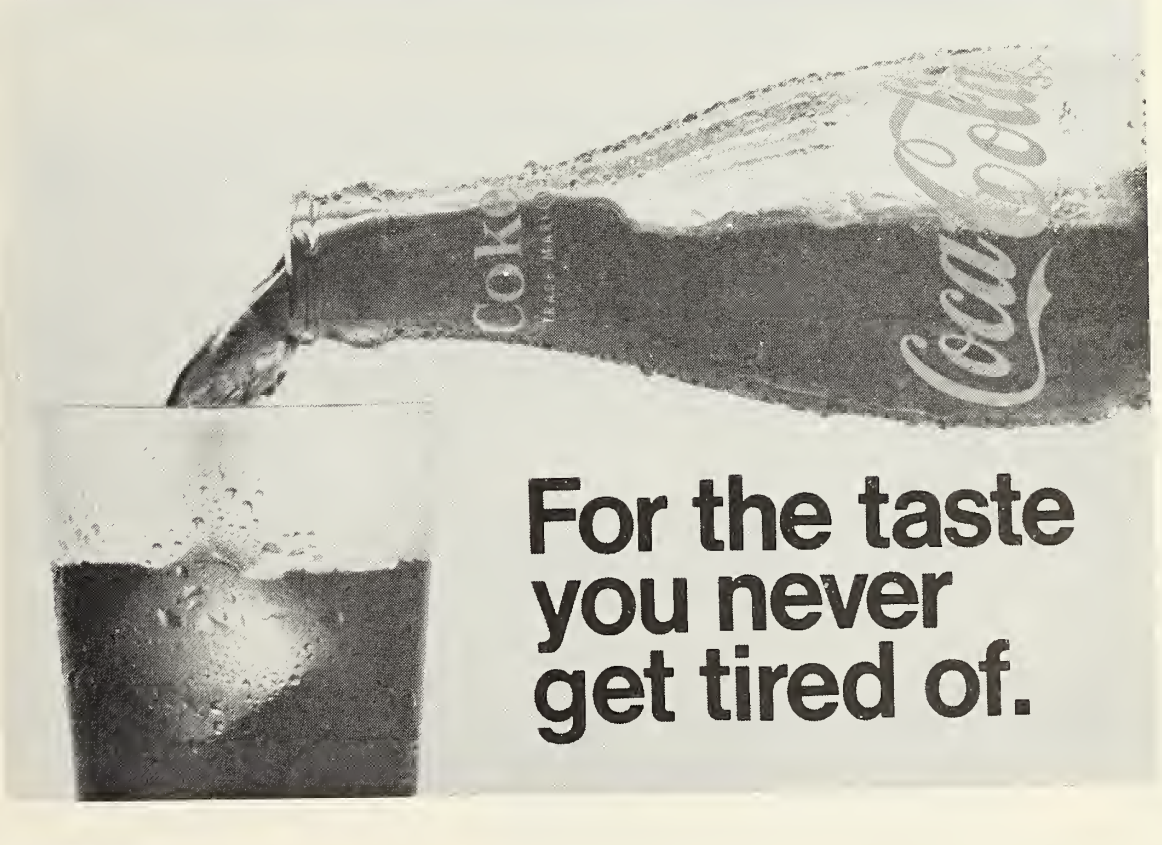

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The first page should list title, the author (or authors), degrees, and any institutional or other credits. Bibliographies should conform to the style of the Quarterly Cumulative Index published by the American Medical Association. This requires in the order given: Name of author, title of article, name of periodicals with volume, page, month—day of month if weekly—and year. Number should be limited to absolute minimum. References should be numbered consecutively in order in which they appear in the text.

LENGTH OF ARTICLES

Ordinary articles should not exceed 3,000 words (approximately 3 printed pages). Under exceptional circumstances only will articles of more than 4,000 words be published.

ILLUSTRATIONS

Illustrations should be numbered consecutively and indicated in the text. The number, indication of the top, and the author's name should be attached to the back of each illustration. Legend should be typed, numbered, and attached to each illustration. Photographs should be clear and distinct; drawings should be made in black ink (preferably India ink) on white paper. For half tones, glossy photographs should be submitted. Connecticut Medicine will bear the cost of printing two cuts accompanying manuscripts submitted for publication. The cost of printing more than two cuts must be borne by the author.

NEWS

Our readers are requested to send in items of news, also *marked* copies of newspapers containing matter of interest to physicians. We shall be glad to know the name of the sender in every instance. All copy should be received one month prior to the expected date of publication.

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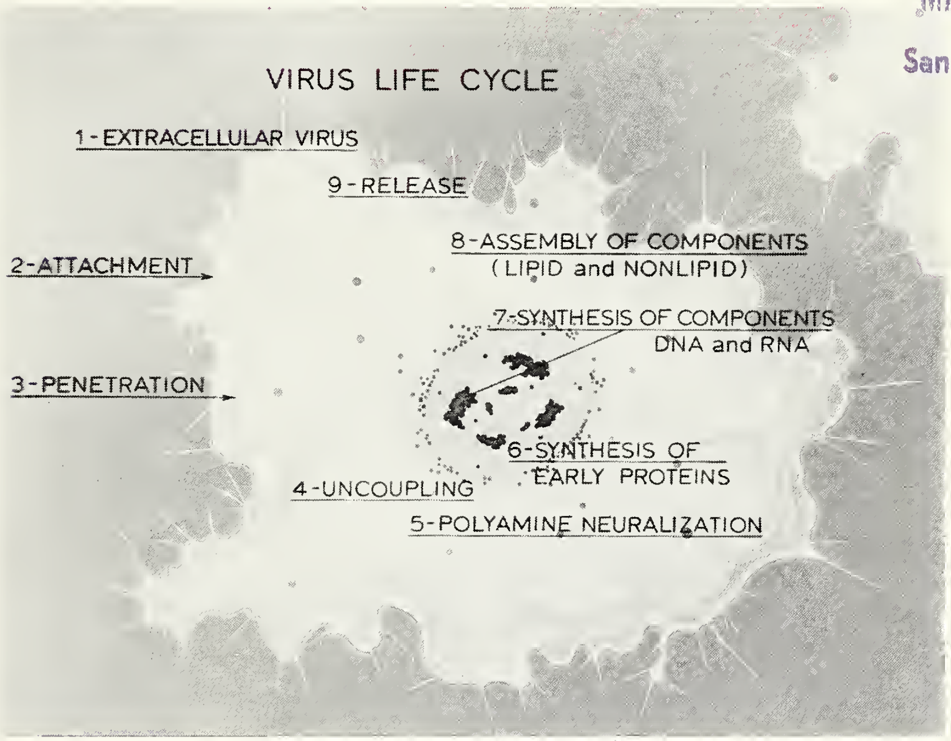
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editorials

Guide-Posts For Workmen's Compensation Commissioners In Cardiovascular Disease

Hellmuth[1] found in Wisconsin that nearly half of the awarded cardiac involvement compensation claims were not medically justified if the criteria for Causality set down by the American Heart Association were applied. One of the victims of such unscientific findings by the Workmen's Compensation Commission turned out to be the patient himself and all cardiac patients who are functional and can and should work. They are potentially employable but over half of the industrial concerns in Wisconsin will no longer hire a new cardiac applicant based largely on the basis of cost of Workmen's Compensation.

He also found among a survey of 123 attorneys that many were concerned with the problem of conflicting medical testimony. Perhaps the greatest assistance to the administrators of Workmen's Compensation Laws could come from securing rather unanimous agreement regarding setting up of essential guideposts for administrators. In fact when Hellmuth suggested this they replied "I am sure that the writer hereof and his associates would be deeply grateful for such assistance".

The rules which Hellmuth formulated as guidelines in the Rules of Practice (published regulations found in most states pertaining to the manner of appearance of witnesses and presenting evidence before the Commissioner) had the following objectives: to clearly define the role of medical testimony on the settling of cardiac claims; to facilitate better interprofessional communication among attorneys, physicians and commissioners; and finally to stress the importance of post-mortem examinations.

The proposed Rules of Practice dealt first with nomenclature and definition of heart disease in its various clinical aspects such as various causes of heart disease and definition of a heart attack and how to differentiate between one caused by unusual strain and one due to natural evolution of the underlying disease. Next was the recognition that heart disease must be viewed from its etiologic, anatomical, physiological and degree of functional impairment. Those are all time honored concepts which cardiologists have used in fully encompassing a complete cardiac diagnosis. We all realize how difficult it is to translate impaired cardiac function as a contributory factor with the statutory meaning of disability. But certainly if one follows the guidelines on functional capacity for evaluating cardiac impairment it should prove helpful as a basis for administrative rating of permanent disability.

Such rules would not alter the advisory system nor necessitate a change in the statutes, because they were designed to be addressed primarily to physicians with explanatory medical terms, and ideology for the attorneys, commissioners and the non-professional persons such for example as adjusters.

One plea is to suggest to the commissioner at any time after the application for adjustment has been filed either before or after the hearing, that he select one or more physicians who are certified by the subspecialty Board of Cardiovascular Disease of the Board of Internal Medicine to examine the patient or to review medical data. Such physician could then prepare a written report to the commissioners and furnished to all parties in interest. Clearly the Commissioner would not require expert opinions unless the medical testimony is in conflict.

The philosophy of Workmen's Compensation is embodied in its main objective to assist the worker

THE COVER

THE life cycle of a virus as it occurs in the infection of a mammalian cell. With most viruses cell lysis follows the maturation of virus, but some viruses multiply within the cell and are released without apparent injury to the cell. Others, such as tumor virus, cause excessive proliferation of cells.

in case of accident in an industrial environment. But if this is the intent of the law, then compensation for natural disease such as atherosclerotic coronary disease, and other degenerative diseases including diabetes, must ultimately come to be handled outside of Workmen's Compensation. The principle reason for this conviction is that there is no scientific evidence to indicate that for example coronary artery disease is in any measure or form actually caused by employment. Furthermore the very few cases of myocardial infarction claimed to be caused by unusual effort or strain would become much fewer if the criteria laid down for causality would be followed.[2]

Thus stress or strain that is medically determined to be definitely unusual and excessive for the individual may cause aggravation or "lighting up" of preexisting cardiac disease in the form of an acute coronary episode. But unusual may not be excessive and very precise definition of these terms and careful search in the patients habitual living is needed to decide whether the exertion is a precipitating factor related to the occurrence of an attack or coincidental with the attack on or off the job. It must not be inferred that the employment per se "caused" the incident. If there was excessive exertion (medically determined for each individual) which occurred during employment and followed immediately during or soon after by symptoms and signs of an acute coronary episode there is a reasonable assumption of work connected causal relationship, not of the underlying disease but of the acute episode.

It is good doctrine to realize that causality is the most important concept and that causality rests on a basis of proof of a triad, unusual and excessive strain arising out of employment, unusual and excessive strain in the course of the employment, and the acute coronary episode itself. There is little doubt that the carefully considered workable definitions of Hellmuth will help to eliminate confusing medical terms and guide physicians in presenting testimony that is as lucid and specific as present medical science will allow in determination of causality.

The physician who is thoroughly knowledgeable in the field of heart disease can contribute much to the fair settlement of a claim. While the certified specialist has consistently reliable access to the latest sources of information in a given field and can contribute most to resolving conflicting medical testimony, it cannot be denied that some physicians not so certified are knowledgeable also and could qualify for this purpose in a court of law. As far as the attending physician is concerned his most important role is in presenting objective factual medical information about his patient guided by criteria as laid down for a complete medical diagnosis.[3]

The final point Hellmuth pleads for and we should all strive for is to make autopsies medically mandatory to be performed as a matter of course. Whether they can ever be made mandatory by statute is doubtful, but their importance cannot be stressed strongly enough. Evidence may turn on the results of an autopsy. At the very least it may confirm or deny a provisional diagnosis. At the most they can contribute greatly to the sum of scientific knowledge about causality and employment and lay a precedent for future judgments.

L.H.N.

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The Gap Between Clinical And Pathological Recognition Of Pulmonary Embolism

While studying the fate of experimentally induced autologous peripheral venous thrombi released to the pulmonary circulation in dogs, Freiman, Suyemoto and Wessler[1] noted that some of the residues observed weeks to months after the embolic episode were identifiable as traces of organized thrombi closely resembling similar traces observed in human pulmonary arteries at the autopsy table. Some of these lesions in the dog were so minute that they might well have been overlooked if the index of suspicion had not been high and if a deliberate and meticulous search for them had been made.

The probable fact is that on routine post-mortem examinations the pulmonary arteries are only too rarely inspected adequately.[2] With experiences in the dog as a background, Freiman was led to study 61 human post-mortems for evidence similar to what they found in dogs. They made sure to search arteries as far out as branches 2 mm in external diameter. They carefully studied by the microscope, arterial lesions suspected of being embolic in origin and eliminated post-mortem clot from consideration. One assumption they did make was that all thrombi of the pulmonary arteries unrelated to atheromatous placques to be embolic.

As keen pathologists they used the following evidence of ante-mortem origin: presence within the thrombus of interlacing platelet lines or surface deposition of platelet material usually intermingled with some fibrin and white cells, both of these phenomena indicate exposure to flowing blood either at the time of formation of the thrombus or subsequently during propagation or embolization; evidence of displacement of the site of origin such as coiling and unfolding; presence of branches or venous valve markings related to corresponding structures in the pulmonary arteries; occurrence of organization in the thrombus such as whether or not it was grossly adherent to the arterial wall, which provided additional important clues. Finally was the search for intraluminal webs, strings, and fibrous bands since they can be interpreted as organized post-embolic residua.

With such careful pathologic criteria, the authors found that 39 out of 61 cases revealed thrombi of various sizes from massive emboli occluding the pulmonary arteries to minute adherent and barely visible fragments. Of the 39 only 17 were sufficiently obvious to be recognized readily in routine gross examinations. In 22 patients emboli were represented by traces easily overlooked if a careful search was not being made.

These figures probably represent an accurate sampling of the autopsy material in general. In primary cardiovascular disease emboli occur in somewhat less than half, in malignant tumors in about one-fifth. But the striking point is that of the whole series of 39 autopsies showing pulmonary emboli only three were diagnosed clinically and these were large emboli readily observable and two showed clinical pulmonary infarction. The remaining 36 were truly "silent". When we compare these figures with the average incidence of pulmonary embolism in routinely performed adult autopsies—about 10 per cent—it becomes clear that the discrepancy is due for the most part to criteria used in diagnosing pulmonary emboli, but also differences in the patient population.

As the criteria for diagnosis of pulmonary embolism are enlarged, then reports of 15 per cent or 18 per cent are encountered. Before the special search was made at the Beth Israel Hospital, 33 per cent of pulmonary emboli were uncovered. As the criteria were enlarged, the study revealed instead a 64 per cent incidence. One is impelled to conclude that more rigid criteria which led to better care of patients account for the increased figure of incidence.[3]

We know from experience on dogs that the emboli actually found are not at all indicative of the number of emboli that occurred. When dogs are subjected to pulmonary embolization with serum induced thrombi, most of the thrombus undergoes lysis during the first few days. It is the portion that cannot be lysed which undergoes organization and eventual shrinkage. After a period of weeks to months only small organized nubbins or in some cases no visible evidence of embolization can be found even though the pulmonary artery may originally have been filled with thrombi.

Human thrombo-emboli are probably disposed of in similar fashion and the wide variation in one degree of organization of the residua sometimes found within the same patient as the occurrence of more recent thrombi entangled in old webs frequently provides evidence that more than one embolic episode has occurred. Besides, some emboli may undergo complete lysis or may eventually become incorporated into the vessel wall. For these reasons we must conclude that the frequency of embolic episodes may very well be even greater than the autopsy data indicate.

It is probable that refinement and more widespread use of clinical aids in diagnosis as venography, pulmonary angiography and lung scanning with radioactive tracers, serum enzyme determinations, measurements of pulmonary gas exchanges and studies of the mechanisms of respiration will eventually aid in narrowing the gap between clinical and pathological recognition of pulmonary thrombo-embolism.

Patients in one way are fortunate that in spite of the high frequency of pulmonary embolism only a small fraction of them present clinical manifestations of these episodes. Can this be due to the efficacy of their fibrinolytic mechanism which quickly disposes of the clots as it does in the dog? What about the low index of suspicion as a result of which some cases of even extensive pulmonary embolism without infarction are not recognized before death? Certainly not all, even massive embolism are obvious and produce no more than transient alterations in blood pressure, heart rate or other vital signs.

Freiman's studies however should alert us to the frequency of pulmonary embolism occurring in heart and other medical cases since a high index of suspicion can set into motion preventive and therapeutic measures which can reduce mortality as well as morbidity from thrombo-embolism.

L.H.N.

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Recognizing Emphysema By Physical Diagnosis

"I for a long time thought it very uncommon because I had observed only a few cases of it; but since I have made use of the stethoscope I have verified its existence as well in the living as in the dead subject and am led to consider it by no means infrequent." R. T. H. Laennec.[1]

Now that emphysema is increasing in incidence and importance much more so than in Laennec's day how adept is the modern physician in its recognition by physical diagnosis. Fletcher[2] had already encountered extreme variation and error in detecting emphysema among patients with pneumoconiosis. How justified are we in our belief that we can diagnose emphysema with confidence on clinical grounds.

Schneider[3] attempted to analyze objectively the proficiency of a group of physicians engaged in private practice of medicine in their ability to recognize obstructive emphysema by physical signs alone. The 9 physicians tested had contact with patients with diverse disorders and made frequent evaluations for disability, insurability and rehabilitation. Five of the 9 physicians were diplomates of the Board of Internal Medicine, and 3 were eligible to take the Board Examinations. Thirteen patients with obstructive emphysema were examined by the 9 physicians for a total of 84 examinations. The existence of obstructive emphysema in these patients uncomplicated by pneumoconiosis was established by using forced expiratory volume and maximal voluntary ventilation. They rightly did not use the fraction of residual volume/total lung capacity because the increase in this ratio occurs also in aging subjects and at any rate is too difficult to estimate.[4]

The physicians were given 14 signs to look for, a stethoscope, and a tape measure. The idea was twofold: first to determine proficiency in recognizing the signs and second to assess the relative importance of the various signs that the physicians used to conclude whether emphysema was present or absent. Stated in another way what signs did the physicians rely upon and how correct were their concepts.

It developed that there were striking variations among the examiners in their capacity to detect individual signs. For example, the barrel deformity was recognized in 64 examinations and missed in 20. There was a 23 per cent disagreement as regards the existence of hyperresonance. There was even extreme variability in determining chest expansion by a tape measure which we ordinarily would assume to be an accurate and reproducible item. This variability was even found in normal subject with a mean of 2.29 inches but the range was given between 1-3 inches by the different physicians. Diminution of breath sounds fundamentally the most important single index, was utilized 8th by the examiners to diagnose emphysema. Finally the 2 signs the physicians apparently thought most indicative of emphysema, liver dullness and decreased diaphragmatic movement actually showed no statistical important relation to the existence of emphysema.

What seems to have happened to "the watchful eye, the alert ear, the tactile finger and the logical mind which correlates the facts obtained through all these avenues of information to reach an exact diagnosis"?[5] To be sure the old masters were of necessity forced to rely heavily upon their capacities to perceive physical signs of disease in the living subject. The logical mind of the modern physician also frequently utilizes "facts" obtained through physical examination to arrive at a definitive diagnosis. Laboratory data have helped to sharpen his examination. The electrocardiogram has clarified for us and made it possible to recognize many arrhythmias at the bedside. Likewise respiratory function studies have contributed greatly to the meaning of the signs at the bedside that justify the diagnosis of emphysema.

It is of interest in Schneider's study that our contemporaries showed preferential use of signs perhaps unconsciously that contrasted substantially from their apparent worth. Have we come to rely on the laboratory so much that our acuteness in physical diagnosis is somewhat blunted? In emphysema there are authentic guides to its recognition. They can be readily elicited. All that remains is an understanding by the examiner of the pathology in the lung, the physiological disturbances resulting in emphysema and a certain amount of examiner's skill and care with which the examination is conducted.

The sign Laennec observed in emphysema "the respiratory murmur is inaudible over the greater part of the chest and is very feeble where it is audible" — that is diminution of breath sounds shows the closest statistical relationship with physiologic severity and deserved much greater emphasis than given it by physicians in conducting their examinations. Why impaired breath sounds, why the barrel chest, why decreased chest expansion, why impaired cardiac dullness and absence of apical cardiac impulses, why use of accessory muscles of respiration, why diminished diaphragmatic excursion, why finally cyanosis?

The answer to these questions lies in the nature of emphysema. Literally the term means a lung puffed up with air. It is overinflated, its elasticity is lost, the alveoli are dilated, many of the septa are destroyed giving rise to large bullae. As the alveolar walls thin out, there is a decrease in the capillary bed and this interferes with oxygenation. Compensatory or secondary polycythemia develops. There is increased viscosity of the blood and strain on the right heart which leads to hypertrophy.

If the lung tissue is decreased and amount of air is increased, the patient becomes dyspnoeic, inspiration is short, expiration is long because the elastic recoil is poor. Thus it looks as if the patient had taken an extremely deep breath and then held it. The ribs may be almost horizontal, the costal angle is wide, the sternum is pushed forward and the thoracic spine may show exaggerated bowing. The antero-posterior diameter becomes equal or exceeds the transverse diameter giving the classic barrel chest deformity.

Obviously, if with inspiration, the thoracic cage expands but slightly the lungs are in expansion, the cardiac dullness is diminished, the diaphragms are pushed downward, and the thoracic cage is pulled up as a unit by accessory muscles of respiration in the neck. The shoulders may be elevated and held somewhat forward and the clavicles and supraclavicular fossa are unduly prominent.

Of course the lack of expansion can be confirmed by palpation, and by a tape measure. There is decreased fremitus because of excessive amount of air in the lungs and hyperresonant note on percussion. Auscultation will reveal feeble and distant breath sounds because little air is being exchanged and the large air containing sacs interfere with the transmission of sound. Inspiration is almost inaudible, short, expiration long, harsh and low pitched. The heart sounds are distant and P2 accentuated.[6]

If the physicians in Schneider's experiment had familiarized themselves with the basic anatomical and physiological disturbances in emphysema, there is little doubt their physical diagnostic acumen would be sharpened and their scoring would be enhanced. This approach would sharpen the art of physical diagnosis in the recognition of emphysema. It would be interesting to repeat Schneider's study on the art of physical diagnosis in another group of physicians who first familiarized themselves with the underlying structural and functional alterations that are present in emphysema. It doesn't require too much insight to predict that their scoring would be much higher. What Schneider's study reveals is not the need for more laboratory diagnoses for emphysema as much as a more alert knowledgeable physical diagnostician.

L.H.N.

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Enzyme Induction: Therapeutic Uses

Newborn infants are unable to detoxify drugs adequately by conjugation with glucuronic acid in the liver because glucuronyl transferase in the liver is depressed. As a result of deficiency of this enzyme which also catalyzes the conjugation of bilirubin, the infant can develop jaundice. Another consequence of this deficiency is an increased sensitivity to the toxic effects of such drugs as chloramphenicol that are normally metabolized to glucuronides.

Like many other drug metabolizing enzymes, glucuronyl transferase is localized in the smooth endoplasmic reticulum of liver parenchymal cells. Treatment with barbiturates and other drugs can cause a striking proliferation of the endoplasmic reticulum and a marked increase in the activity of many drug metabolizing enzymes.[1] This action of phenobarbital has been shown to increase the metabolism of the coumarins and therefore to interfere with maintenance of an appropriate prothrombin time in patients receiving anti-coagulant therapy.[2] At the same time of course this is the mechanism whereby patients develop tolerance to barbiturates, glutethimide and meprobamate since they are metabolized by glucuronyl transferase.

If glucuronyl transferase production is increased by administration of phenobarbital, then this drug should be useful whenever the enzyme is deficient. Jaffe, et al[3] describe their attempt to increase the activity of glucuronyl transferase in a hyperbilirubinemic infant by treating it with phenobarbital. As a reflection of impaired glucuronide synthesis the infant was unable to conjugate its bilirubin and consequently developed increased concentration of unconjugated bilirubin in the blood with manifest jaundice.

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Congenital non-obstructive non-hemolytic jaundice which is thought to be due to a functional impairment of the glucuronyl transferase system presents a particularly serious and difficult problem in treatment. Thus far efforts to increase glucuronyl transferase activity in infants by means of drugs have been unsuccessful. Before Jaffe undertook to treat their patients with phenobarbital, they engaged in preliminary experiments on newborn rats and mice to determine if their livers could be stimulated to form glucuronyl transferase by phenobarbital. The results were positive in that the animal livers, stimulated by phenobarbital, were then able to form glucuronide of sulphadimethoxane.

After such preliminary experiments, Jaffe, et al injected phenobarbital in the jaundiced infant, obtained a remission of jaundice and a decrease in blood bilirubin levels. Indirect evidence for increased activity of glucuronyl transferase in these infants treated with phenobarbital was also obtained by measurements of the amount of salicylamide and salicylates excreted as glucuronides in the urine. The results indicate beyond doubt that in infants with a deficient glucuronide forming capacity before treatment, administration of phenobarbital can be expected to eliminate the deficiency and increase the capacity to bind bilirubin to the normal range.

The result reported by Jaffe, et al are certainly encouraging enough to warrant this approach in other situations. Since the endoplasmic reticulum of liver cells contains steroid metabolizing enzymes, we must think of the possibility of using phenobarbital in the treatment of disorders resulting from over production of steroid hormones as for example in Cushing's disease. Phenobarbital happens to have an excellent record of safety when administered chronically over long periods of time. However very little is still known about the consequences that may ensue from induction of proliferation of the endoplasmic reticulum.

The finding that drug administration alters the metabolism of hormones, vitamins and drugs raises the question as to whether we should look at this phenomenon as an alteration of normal homeostasis in response to a foreign chemical or whether some of the responses are toxic effects of the drug. Certainly in liver disease drugs are much more toxic than in the normal state because of impaired ability of the liver to bind toxic substances by the glucuronyl transferase enzyme system. When the liver is otherwise normal as in the case of congenital non-obstructive non-hemolytic anemia, phenobarbital is certainly useful. In other situations where we depend upon a drug for a necessary physiologic state as we do with coumarins, phenobarbital through its enzyme induction ability would be contra-indicated.

L.H.N.

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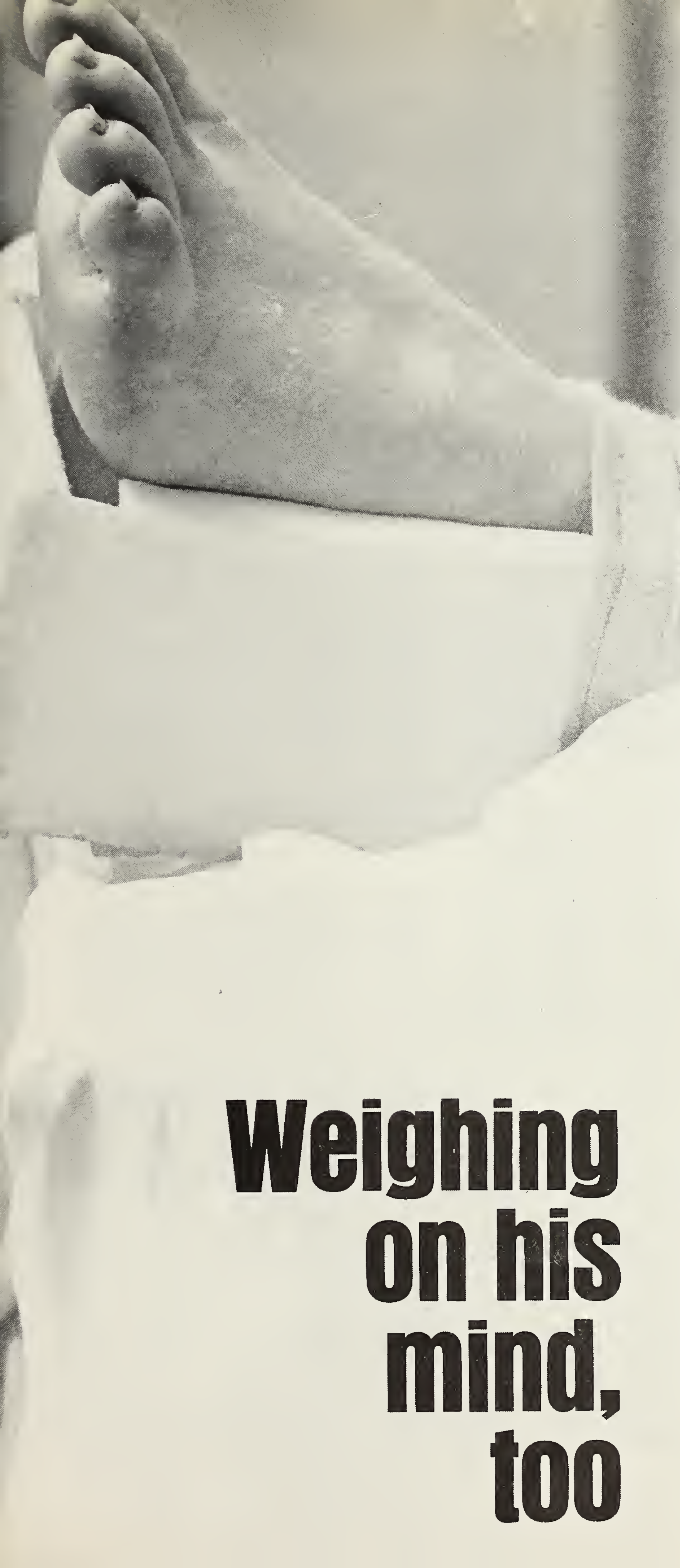
Artificial Materials In Surgery.[1] Basic Principles

The basic problems attendant on the implantation of prosthetic materials in all the surgical disciplines become clear when we consider what happens in the healing of wounds when a surgical incision is coapted by sutures. Here the noxious stimulus is the tissue injury caused by the passage of an incising instrument and healing then takes place by the process of inflammation which is always a healing response of the body triggered by a variety of noxious stimuli.[1]

Most surgeons agree with the assumption that least reacting suture material allows for best wound healing. But the question remains as to what degree of inflammation leads to optimal wound healing. Is inflammatory response to a minimal injury inflicted by a clean surgical wound incision "optimal"? What about biological reactivity of suture material used to coapt surgical incisions? Could this be better than if the material was really biologically inert. For example, Prudden believes that cartilage powder inserted into a wound hastens fibrosis and rate at which wound strength increases with time. And Wu[2] recently demonstrated the same thing for aluminum sutures in which they believe the process is bioelectric rather than chemical.

One of the major problems concerning implantation of artificial materials in surgery then is to define optimal healing or "tissue acceptance" of the material. Two other problems arising from the use of artificial materials are determined by the nature of the healing response. One is rejection of the material, and another the complications of healing. Tissues have no particular desire to accept any implanted foreign material. They will reject them, first by destroying the non autologous implant if they can dissolve and absorb it. If the implanted material is non-absorbable, the tissue simply do not accept it because it is foreign to the nature of the tissue organ or body. Then a surrounding



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Precautions: Keep out of reach of children. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate may result in dependence or habituation in susceptible persons—as ex-addicts, alcoholics, severe psychoneurotics. Withdraw gradually after prolonged high dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance. If drowsiness, ataxia or visual disturbances occur, reduce dose. If symptoms persist, caution patients against operating machinery or driving. Give cautiously to patients with suicidal tendencies. Treat attempted suicide with immediate gastric lavage and appropriate supportive therapy

Side Effects: Ethoheptazine and aspirin may occasionally cause nausea, vomiting, epigastric distress, and rarely dizziness and CNS depression. Overdosage may result in salicylate intoxication. Meprobamate rarely causes allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. Meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioedema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. A few cases of leukopenia, usually transient, have been reported following prolonged dosage. Rarely, cases of aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported; almost always, in the presence of known toxic agents.

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capsule is laid down, the noxious stimulus ceases to exist, a "tissue truce is declared" and the foreign body is allowed to remain "rejected" and incarcerated within its "custom-made cell". Such implant is now considered successful since it can continue to function as a suture, a prosthesis to conduct blood, a check valve to prevent reflux of blood in a cardiac chamber, or it can continue to supply electrical impulses for triggering the myocardium, the detrusor muscle, or the carotid sinus nerve.

If on the other hand the tissues are unable to wall off the noxious stimulus, the body will produce a significant cellular infiltration which is likely to become infected leading ultimately to extrusion of the implant. It seems clear that all artificial materials implanted into the body undergo a degree of rejection varying from simple encapsulation which is clinically acceptable to a violent process of extrusion. We must therefore scrutinize the implantation of artificial materials in terms of the philosophy which governs the entire field of surgery: will the overall trauma of this specific operative intervention be justified by the degree and duration of the physiologic gain which will result.

The biologic specifications for a clinically successful implant of an artificial material becomes clearer.[1] The implant must exert no significant deleterious effect on the host.[2] The host must exert no significant deleterious effect on the implant.[3] The implant must function adequately. These conditions are functions of time and of total risk. They must be able to operate for a length of time consistent with the duration of the fundamental need. The total risk of implantation must be considered in relation to the seriousness of the underlying offending pathologic conditions.

There are presently many classes of materials for a variety of conditions. They are metallic, solid plastics, and porous plastics and textiles. The solid metals are used as implants in orthopedic surgery. They are pure metals like titanium, zirconium, tantalum and alloys of steel, cobalt and titanium. The solid plastic prosthesis are used both for permanent and transient implants. The ultimate fate of textile prostheses depend upon the biologic reactivity of the basic material as well as the specific sites of implantation and the porosity of the prosthesis. Some prostheses like implantable cardiac pacemakers do have unacceptable elements and are coated with a silicone material which effectively insulates the tissue against deleterious effects of the otherwise offensive elements.

The greatest impetus to the use of foreign bodies in surgery followed the invention of the permeable arterial protheses by Voorhees, Jareki and Blakmore in 1952.[3] The arterial prosthesis today represents the most successful substitution by a foreign body for a soft tissue structure in the entire history of surgery. The second great impetus in the development of functionally acceptable foreign bodies was the invention of a variety of polymers known as plastics and rubbers of low biological reactivity and of a variety of physical properties approaching those of the soft tissues themselves.

During the past decade the investigation into the use of artificial materials in surgery has blossomed into a new technology of which one by product is as Gallie pointed out, an increasing amount of surgery required to remove the prostheses. It should be pointed out that artificial materials are implanted today for more than the mere reinforcement functions of yesterday: form buttress, conduit, hydraulic valve and electrical impulse. If one wishes to indulge in fantasy there is no limit to tomorrows function of permanent implants, blood pumping, gaseous exchange, metabolic substitutions for the biologic mechanisms of plasma clearance, chemical synthesis and what else?

There are now permanent implantation for function in every system of the body, in heart and arteries, respiratory system, digestive system, kidney ureter, bladder urethra, the nervous system, special senses, soft tissues, cosmesis and much more.

L.H.N.

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Solving The Problem Of Blood Need, Transfusions: Dogma Or Fact

Until the recent months there has been a serious problem of blood requirement for heart surgery. The need to collect from 15 to 30 units of a single type of compatible blood on the day of surgery was a significant consideration in logistics, in time needed, in cost, and to degree wasteful since the heparinized blood not immediately used had to be discarded. There was also signficant medical problems incident to the use of large blood volumes. One was a higher incidence of serum hepatitis, another hemorrhage associated with transfusion, sensitization and inter-donor incompatibility. In other

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*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

Indications: 1. Functional fatigue such as that often associated with: a depressing life experience or stressful time of life; advancing years; convalescence; limited activity or confinement. 2. Poor appetite and vitamin-mineral deficiency as they occur in: patients having faulty eating habits; geriatric patients who are losing interest in food; patients convalescing from debilitating illness or surgery.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

Side effects: Reports of overstimulation have been rare. Patients who are known to be unduly sensitive to the effects of stimulant drugs should be observed carefully in the initial stages of treatment.

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words the technical advances required of extracorporeal circulation had gone beyond the confines of existent medical and hematologic knowledge.

To alleviate this problem of blood requirement for heart surgery, a small volume oxygenator was devised which was subsequently adapted for procedures of shorter durations using a commercially available disposable plastic oxygenator. Then a low pressure relatively atraumatic suction apparatus was developed which permitted the return of blood to the extra corporeal circuit. Then an attempt was made to use stored blood fibrinogen concentrates, and an anti-fibrinolytic agent epsilon amino caproic acid was tried in attempts to reduce blood loss. This of course reduced the problem of blood need in heart surgery but did not eliminate it.

In 1960 Panico and Neptune [1] introduced a practice of hemodilution in which the primary volume consisted of a mixture of blood and crystalloid solution. Although such a practice was not without its challenging medical problems, it was a departure from previous techniques and an addition to our search for solving blood need problems. Added to it was the practice of controlled deliberate hypotension during surgery and treatment of shock with ganglionic blocking agents instead of vasopressors. Such thinking brought us face to face with general concepts relevant to maintaining satisfactory organ and tissue perfusion in hypotension and shock. The practice of partial hemodilution received reassuring information from animal experiments, but more importantly from an experience with over 600 cases in which partial hemodilution in which a mixture of blood and crystalloid solids was used as reported by Paton, Roe, Neville, DeWall, Lillehei and others.[3]

It was only natural that these results should have been extended to absolute hemodilution. In 1964, Cooley, et al[2] tried this method in seven cases of heart surgery, all Jehovah Witnesses. One patient died from post-operative bleeding but the condition of the six survivors was reported as excellent. Unfortunately there were no vital organ functions studied. This and other experiences with more marked decrease in red cell mass raised the question what is the safe level of hematocrit which a patient can tolerate when his shed blood is replaced with non-hematogenous fluids.

Such information could have a significant bearing on medical practice as well as surgery, particularly in the use of blood transfusions and the emergency treatment of traumatic and hemorrhagic shock. These cases are probably more common than those requiring open heart surgery and are equally subject to the complications from blood transfusions such as hemolytic reactions, allergic reactions and sensitizations, as well as being threatened with viral hepatitis and malaria. Obviously such transfusion complications would be eliminated if expansion of blood volume could be achieved without blood. Using colloid plasma expanders is known to be hazardous since it can be associated with a hemorrhagic diathesis. Finally there is the patient who has a rare blood type which is difficult or impossible to cross-match in emergency situations.

Gollub and Bailey[3] have just described the unusual challenges in management of patients during the operative period of open heart surgery and during the post-operative period particularly with respect to maintaining proper fluid balance. In some patients they used the extra-corporeal apparatus with minimal balance requirements and in short cases the plastic oxygenator bag. An alternative was the use of the newly developed "single-pass" oxygenator which requires only 1200 m.l. of total primary fluid. Heparin antagonism when present was overcome by protamine and after complete hemostasis had been established a judicious portion of the extra-corporeal circuit was returned to the patient before stopping the pump and disengaging the circuit.

The determined blood volume balance was somewhat lower than expected after one to two hours post-operative, but no attempt was made to restore it to values before the operation. Furthermore, careful watch of the blood pressure, pulse, venous pressure, urine output was continually monitored as a guide for treatment. Fluid replacement in the first 12 hours was in the form of lactated Ringer's solution. If necessary after this colloid plasma expander was employed to prevent hypotension since there was a marked tendency for hypovolemic shock to develop via excessive urine flow. But then the hematocrit began to rise. With careful watching there was no real difficulty in the maintenance of a proper fluid balance. A final feature was the tendency toward hypokalemia during the operation and in the post-operative period requiring potassium supplementation via the intravenous route. This reversed the tendency towards poor cardiac function.

There were certain general clinical features showed by all patients: apparent absence of fear, large volume diuresis produced by fluid administration, marked mucous membrane pallor and cutaneous pallor in the post-operative period. All complained of weakness, fatigue, and inability to concentrate and the average hospital stay was prolonged by about a week.

Certain general principles emerge from this study in a group of volunteers who experienced a profound reduction of red cell mass in the face of major surgical trauma. In spite of severe acute decrease of blood cell mass to a hematocrit of 20 or lower this did not jeopardize survival nor produce permanent morbidity. It is the maintenance of blood volume which is the significant factor in the prevention of morbidity and mortality.

The final question for us physicians is whether this experience is applicable to the treatment of other types of hypovolemia or hemorrhage. The hematocrit value decrease to 20 or lower seems well tolerated even following major trauma and when healing is not adversely affected. The immediate volume restoration by crystalloid solutions would appear to be safe and practical provided careful attention is given to vital signs that Golub and Bailey followed so successfully.

But what happens in patients who have ischemic hearts, brains, kidneys, mesentery is quite unknown, so that we must be guarded about the physiological advantages of blood volume replacement by crystalloid solutions in patients with arterial disease. Then we must not forget the increased cost incident to large numbers of laboratory estimations as well as the prolonged hospital stay. Finally we still need to know how long post-hospital convalescence is prolonged in these patients as compared to others whose hematocrit was kept well above the critical levels in the post-operative period with the use of blood.

L.H.N.

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Imprinting And Primary Socialization

The name imprinting has been given to the process which results in what is a lasting identification of parent or refuge. The term critical period defines the limited span in early life during which imprinting is possible. Lorenz[1] was drawn to this phenomenon after he had occasion to allow a number of geese to hatch inside his home. Here he observed them during the first days of life and was himself their only living contact. He released them into his yard and admonished them to find their mother, but whenever he appeared they ran to him in preferenec to their own parent.

Not only geese but many other birds have during the first few hours of life the same compulsion to give attention to, and follow, a moving object which will become their refuge in time of anxiety later in life. This following reaction reaches its peak at a special age in many birds being 11 to 14 hours in ducks.

The imprinting can be modified by many factors such as the making of a noise which is a very effective imprinting object for a duck, while size, shape and appearance of the object is less so. The strength if imprinting seems to be surprisingly increased during the critical period by interposing an electric shock between the duckling and the moving object. The critical period of imprinting is ended by the emergence of a fear reaction at the approach of a strange person or object when flight towards the imprinting figure takes place as a refuge and protection.

The imprinting phenomenon is found in other animals. In the lamb it occurs during the first few days as is seen from the rhyme "Mary had a little lamb". In puppies human handling socializes them in about 7 weeks. The wolf's imprinting period ends almost as soon as the eyes can open. If brought into human company before this they are easily domesticated. If his eyes open upon the mother or litter mates he will remain a wild animal.

The social identity of the child is fostered by mutual stimulation between parent and offspring. A goat will refuse to nurse a newborn kid which has been removed from the mother for 40 minutes in the first day of its life. The mother however will nurse any kid brought to it immediately after delivery. A lamb returned to the flock after a day or two in human company will be promptly rejected by the flock which considers the addition alien to it. It is an example where imprinting of a human is poorly tolerated by the animal flock.[2]

In primate socialization, an infant monkey raised with a cloth mother[5] will turn to it as a refuge in time of anxiety, but when they grow to adulthood they are completely incapacitated for social and sexual adjustment in a monkey colony. They will take positions at the bottom of the pecking order and neither male nor female is able to carry out effective sexual activity. Occasionally a normal male may impregnate a female who has been raised with a mother surrogate but the offspring of this liaison has a very hard time. The mother proves incapable of giving what for a long time we have felt was instinctually determines normal maternal care. The emotionally damaged mother fights off the infant's approaches, refuses to nurse him and in other ways indicates that the deprivation of her own infancy has made her into a bad mother.

If the infant survives he may turn out surprisingly well despite his mother's abusive care. Even if a monkey is raised with a mother surrogate, it can be brought nearly to normal function in the colony by as little as a few minutes each day of interaction, romping or playing with other monkeys of their own age. This exposure to active members of the same species leads to learning of social and sexual roles.

The imprinting process is the most primitive identification by the young animal of the species to which he belongs and to which he will turn for cooperative members in those varieties of social interaction which are typical of the species. Once an animal is imprinted it will hold on with great tenacity to the effects of primary socialization.

The counterpart of primary socialization in man is not yet clear. We know that during the first few weeks or months of life the infant identifies the human form of the people who will give him care and that by six months he has precisely identified the human form of the people who will give care and especially the one important person, usually his mother. The earliest and most important stage by five to eight weeks is the baby's first smile sure to be answered by a healthy mother with returning smile. The interplay between mother and infant goes on apace and by six months the infant begins to show anxiety when his mother leaves his sight. This is a favorite time for sleep problems to make their appearance.[2] The approach of strangers now is anxiety provoking. This seems to be the counterpart of the anxiety at the approach of others which terminates the critical period of imprinting in certain other animals. It may be said that the period of primary socialization in man extends from six weeks to six months and that these are the critical months.

Primary socialization doesn't always occur smoothly and in fact it can be profoundly disturbed or modified. Provence and Lipton[4] have called attention to the fact that infants without individual care in institutions did not thrive developmentally when compared to others whose first three months of life were spent under adoptive care. Some of the developmental difficulties could be restored if the infants were placed in adoptive homes after one year. However there remained severe residual effects at five to six years of age in the quality of their adaptation to social requirements and in the meaningful give and take with others. Blunted was their capacity for imagination and for the enjoyment of creative activity.

This understimulation of the infant which impairs socialization has been called "privation". Equally devastating may be the interruption of a process of healthy socialization by death or removal of a parent or parent substitute. A child deprived of maternal care may go through stages of immediate protest, a more prolonged depression and final "detachment" and only a degree of adaptation.[5,6] Many children who have readjusted to such loss have paid a heavy price for it.

Bowlby[7] called attention to this phenomenon after examination of the histories of a group of adolescents in trouble who came from bad homes and had obviously defective socialization. The chief features seemed to be an incapacity for interpersonal feeling (the "affectionless child"), impulsive behavior, poor school achievement in spite of an adequate intellect, and stealing, often with surprisingly little concern at being caught. This increased awareness of the importance of privation and maternal deprivation have led to modification of adoption procedures and policies in many areas.

Realizing the character disorders and loss of feeling and imagination which comes from improper primary socialization, we are in a position to ask some searching questions in the quest for maximum utilization and development of our human material. How can we best promote arrangements for newborn infants and their mothers to receive reciprocal stimulation necessary for optimal growth? Is there any dilution of the maternal role which results from her work outside the home? If socialization like imprinting is strengthened during a critical period in infancy by some anxiety, how favorable is this to the ultimate functions as the child grows older? What are the early needs of human children for contact with others of their own age in and out of home, etc., etc.

It is clear that we physicians have much to do to encourage relationships between parents and infants so as to maximally use our knowledge in promoting healthy socialization. Some of this knowledge has come to us from animal work and we can see that much of human behavior has deep biological roots.

L.H.N.

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Walking Through Angina

There is great variability in exercise tolerance among patients with coronary artery disease (CAD) who suffer from angina pectoris (AP). In some the increased exercise tolerance depends on a preceding episode of exercise induced AP. The most complete expression of this phenomenon is the patient who is able to overcome an attack of AP by persisting in the precipitating effort until the pain disappears. After the subsidence of the pain the patient can continue the exercise without distress. A classical description of this phenomenon is found in a letter to William Heberden by an unknown patient: "I have frequently, when in company, borne the pain and continued my pace without indulging it; at which time it has lasted from five to perhaps ten minutes and then gone off".[1] This phenomenon resembles the occurrence of "second wind" in athletes and described as "walking through one's angina."

A very common manifestation of this phenomenon occurs often in the morning when a patient after being brought to a halt one or more times by his angina, is subsequently able to resume the same effort and continue it indefinitely without discomfort. It seems to resemble the improved performance of an athlete after he is thoroughly warmed up. Some have termed it "first hole AP when occurring during a round of golf. Osler described such a patient in 1897.[2] Wenkebach[3] introduced the term "toter punkt" to describe that point during effort when the subject feels like dying before he gets his "second wind". In fact it is not at all uncommon to discover this phenomenon in patients if they are specifically asked about it.

As one might expect differences would appear in the literature about this phenomenon depending upon the patient studied. Some held that if the amount of exercise remains the same the first attack of AP will not make easier the second one. Others found cases in which this phenomenon did exist and was similar to the effect of nitroglycerin in improving exercise tolerance in AP. Price[4] found however that one in every five subjects with AP were of this type if the possibility were kept in mind during history taking.

MacAlpin and Kattus[5] report on their studies of 12 patients of this type. They made them walk on a treadmill to keep exercise steady. They monitored the electrocardiogram and in some patients they studied the coronary arteries by cinecoronaryangiography. Six of the patients had noticed the phenomenon of walking through angina or improving their exercise tolerance after "warming up". Of the eight subjects in this group four had frank occlusions, with clear evidence of collateral channels. Three had strategically placed stenotic lesions but no frank occlusion and no collateral circulation had developed while one case showed both types. The observation on these patients clearly indicate that some patients with AP have a capacity to adapt in a way which permits improvement in exercise tolerance.

The mechanism underlying the phenomenon of walking through an anginal attack or of getting warmed up by a previous anginal attack has profound implications in our approach to the management of these cases. The "walk through" phenomenon in MacAlpin and Kattus patients occurred during a steady state of heart rate and arterial pressure and therefore is unlikely to be due to a decrease in cardiac work and oxygen need since we know that heart rate and blood pressure are major determinants of myocardial oxygen need.[6] It must therefore be due to increased myocardial blood flow and reduced lactic acid and other metabolite accumulation in the myocardial cell.

From the physiology of the warming up process, we have learned that initial contraction of muscles are more largely anerobic with the result that waste products accumulate. Very quickly however local vessels dilate, blood flows through faster and venous return increases. Cardiovascular compensations occur, all of which supply larger volumes of oxygen to muscles and heart. This creates more favorable conditions for diffusion of CO_2 and lactic acid out of muscle and cardiac cells. It could very well be that in CAD lactic acid accumulates too readily in myocardial cells under the demands of certain amounts of exercise and that local vasodilatation in hearts capable of it, which results from the exercise, is what brings the anginal pain to an end as exercise proceeds.

The presence of some form of adaptation to exercise would therefore seem therapeutic with prognostic implications as well. Five of the patients showed striking improvement in anginal symptoms and exercise tolerance while on a program of regular walking exercise. What was equally important was that in two patients who were allowed to lapse in their exercise training, their tolerance for exercise worsened again. Furthermore, the patients who exhibited adaptation to exercise were the ones most likely to benefit by a therapeutic exercise program. This is another way of stating that by exercise training one can discern those patients suffering from AP whose coronary vessels retain an inherent capacity to dilate and perhaps develop collateral circulation.

From psychological point of view exercise training in AP is a way of proving to such patients that their exercise capacity is actually better than they had supposed and that graded exercise is an ex-

Posed by professional model

I'm supposed to get up and do things?

With my heart?

It's entirely natural—and may even be desirable—for the cardiovascular patient to be somewhat anxious about himself.

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cellent method by which to improve the coronary circulation and promote further rehabilitation.

L.H.N.

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Stages In Memory Storage

"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path. . . . . . . .For it has been found in almost all things that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them or they become deranged in some way.—Sir William Harvey.

Shuttleworth[1] in the space of one year has seen patients, four during an attack, lasting for a period of hours, in which there occurs a sudden loss of ability to lay down lasting memory of any kind. During the attack there are no other neurological impairments and all patients recovered completely. This opens up a whole new increasing interest in the nature of memory and makes it possible to speculate on some aspects of the normal memory process.

During the period of amnesia an apparently normal person shows a glassy stare, feels slightly dizzy and staggers somewhat. During the next several hours he is oriented as to person and place, but like a broken phonograph record, he asks what happened?—what happened this morning, what time is it, what day, what date? He remembers not that the doctor examined him, sent him to the hospital. He had had no drugs or alcohol, no previous such experience, no neurological deficits, no hypertension. He lost his memory at 9 A.M. but his digital span was normal, writing was unaffected. During the succeeding few hours memory function began to return and by evening he was considered normal. Four months later he still had complete amnesia for a number of the hours after onset of the attack. There was no recurrence.

This syndrome which has been termed Transient Global Amnesia is probably more common than one would suppose from reading the literature,[2] is obviously a definite and easily recognizable entity. In common with findings in other amnestic syndromes such as that occurring in the first stage of anesthesia, Korsakoffs syndrome, neoplasms, seizure discharges, encephalitis or infarction involving the hippocampal region, these patients retain both remote and immediate memory functions throughout the attack.[3] The preservation of immediate memory makes possible the patients ability to continue to function in a reasonably capable fashion. He can for instance carry on intelligent conversation, drive his car, dial the telephone or transcribe figures at work. The cardinal defect is the total inability to record lasting memory traces so that perceptions and experiences occurring during the attack though held briefly in immediate memory are then lost forever.

If these patients retain immediate memory, that is one lasting for a second to one minute and remote or long term memory lasting perhaps a life time, but have lost recent or short term memory, it appears that we might think of the memory process as a triphasic process. This permits us to speculate on the biomedical basis of memory which biomedical, neurosurgical, and psychological investigation have been pursuing since Korsakoff's observation in 1887.

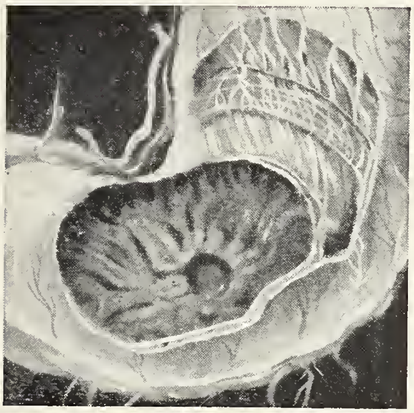
Experiments on mice[4] have revealed three phases in memory. One extends for a number of minutes. The second phase which is inhibited by substances that prevent protein synthesis (puromycin) may extend for several days. The third phase, or long lasting, which can be interfered with only by more diffuse intracerebral damage. As one ascends the phylogenetic scale the duration of these phases becomes shorter but the schema mentioned above can also characterize the human process.

In the short term process there is first transcription of an electrical stimulus within a neuronal network which is then converted into a stable macromolecular form involving synthesis of a coded protein.[5] This process is short. The second phase involves storage of these engrams—long term memory.

In the third phase we have recognized a recall or readout mechanism presumably by transduction back to electrical neuronal activity triggered by an appropriate stimulus.

The span of immediate memory could be affected by spontaneous decay of the trace or by external interference with the trace by new memory information. The trace might become inaccessible so that there is a failure in the readout process. There then might be competition from previous or subsequent learning. Trace interference in im-

In peptic ulcer...



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mediate memory decay seems to increase with aging and may be one of the main factors in the memory impairment of advancing age, along with deterioration of voluntary recovery (readout) of stored material. Most experimental and clinical estimates of the duration of immediate memory in man and primates varies between a few seconds and a minute depending upon the information received.

The neural basis of immediate memory must be extremely complex for it involves pathways between cortex and thalamus for a favorable response. If the information is meaningful it may be recorded for more permanent storage, a function of the second stage of memory. Selective modalities of memory function can be abolished experimentally by bilateral ablation of appropriate areas of the cortex. Ablation of the anterior portion of the first and second temporal convolution will eliminate auditory memory within one second of a presentation of stimulus while leaving visual memory intact. Visual memory can be destroyed by ablating the posterior portion of the second and third temporal convolution.

Immediate memory was found to be normal by Drachman and Arbit[3] in patients with bilateral hippocampal lesions, but severe impairment in patients with short term memory losses in the case described above. The block in this patient then probably occurred in a region of the brain involving also the hippocampal area and involving loss of protein synthesis activity in these specific neurones.

Penfield and Pirot[6] have exhaustively investigated the relationship of large portions of the temporal cortex to the readout mechanism. Remote memory which is not affected in the patients with temporary short term memory loss is probably for the lifetime of the individual. Its readout mechanism (voluntary recall) seems to be the limiting factor for all practical purposes.

It seems clear from an analysis of the characteristic manifestations of the permanent memory loss in the second phase of memory exhibited by the patient described above that human memory can be clinically separated into at least three recording stages, each of which has its own recall mechanism as an integral feature of each stage.

L.H.N.

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Approaching The Cancer Problem

Last year 830,000 persons were under treatment for cancer and there were 540,000 new cases. This means that one-fourth of all people now alive will be found to have cancer during their lifetime. In the male, cancer of the skin, lung, and prostate have about equal distribution. In the female 21.6 per cent is breast cancer, 13 per cent uterine and 11 per cent intestine. Furthermore the five year survival rate has not changed much, still being about 50 per cent in female breast cancer, 90 per cent in skin but has increased somewhat in uterine cancer. Furthermore the concept of a five year cure is fallacious because several kinds of cancer continue to take their toll after five years.

These stark figures leave little basis for optimism that the results of surgery and radiation will be markedly altered in the future. Many have even begun to doubt that earlier and more radical operation and radiation can save 50 per cent instead of the present 33 per cent now cured. Our goal obviously is to cure with elimination of suffering and the mutilation that present therapy entails. This requires on the one hand prophylactic measures, and on the other, medical approaches to eliminate and arrest already established neoplastic disease.

Prophylactic measures do not mean merely early recognition of existing cancer but also recognition of the causes of cancer and knowledge as to recognition of the causes and success in eliminating them. We have, for example, as a profession been too cavalier in dealing with well substantiated data relating lung cancer to cigarette smoking. So have the lay public. To be sure there are large vested interests making a profit out of it such as the tobacco raising farmers, the cigarette companies, the advertising media and even the government itself. Matters of this kind vitiates all our efforts to spread the truth about this dangerous habit and make more urgent the search for therapeutic measures.

The chemotherapeutic agents that are commonly employed such as nitrogen mustard, chlorambucil, cyclophosphamide, busulfan are widely used in tumors of blood elements and methotrexate in choriocarcinoma. Nevertheless we must think of the toxicity and lethality to the patient of these agents as well as benefits achieved from chemotherapy. In the first place, the absence of other therapy such as surgery and radiation and the dire straits of the patient are not adequate reason to employ chemotherapy. Rather must we weigh the possible benefits which must be sufficient to justify the risks of drug toxicity with its consequences of increased suffering, lengthened hospitalization or even mortality. Hiatt[1] points out that in cancer treatment it is most often correct to decide not to use the most recently described drug.

However, the decision not to treat a cancer patient with drugs does not mean we should neglect or abandon the patient or his family. We all know that under circumstances the highest qualities of humanity and compassion are required from the physician.

With the drugs presently available, life can be prolonged in but a small minority as in choriocarcinoma and Burkett's lymphoma found in African children. In these chemotherapy is the approach of choice. In a larger number, suffering, invalidism and hospitalization can be significantly reduced but even then we achieve no more than a temporary remission. Frequent palliation can be obtained in leukemia, Hodgkins, lymphosarcoma. Much less frequent palliation is achieved in some and none in lung, pancreas, renal cell, melanoma, hepatoma, bladder cancer and cancer of the uterine cervix. Prostatic cancer can be held in check better by orchiectomy than by estrogen and occasionally breast cancer by large almost untolerated doses of stilbestrol and by non virilizing androgens. The usefulness and deficiencies of our present chemotherapeutic armamentorium underscores the urgency of continuing cancer research.

Hiatt points out that there is no known genetic or non genetic aberration which is common to all forms of cancer, but we can recognize several widespread defects. One is a loss of contact inhibition, which is manifested by certain mammalian cell lines in tissue culture when they have undergone neoplastic transformation. Normal diploid cells in tissue culture move actively on the surface of the culture vessel until they come in contact with each other at which time locomotion and further growth ceases. The same cell transferred into another culture medium again begins to move, grow and again on contact with another cell, ceases locomotion and growth. Malignant cells do not exhibit contact inhibition but continue to grow and multiply uninhibited by contact. What can it be that holds reproduction in check in the normal cell and that allows reproduction and growth to proceed in the malignant cell.

Several mechanisms might here be operative such as altered host DNA, introduction of new DNA or RNA by a virus or other agent and finally a cytoplasmic change in the membrane itself. This last would be a non-chromosomal genetic change which has several precedents; such as profound changes that take place in bacterial cell wall that replicate themselves; cell surface changes in paramecium occur as a result of environmental changes independent of chromosonal alterations that are heritable for many generations. Finally in higher organisms the events of differentiation lead to extraordinarily variable characteristics in cells all having the same genome and yet each capable of reproducing itself such as a liver cell.

The process of differentiation from a fertilized egg to a variety of cells, although stable may in fact be reversible up to a rather late stage and this encourages us to hope that some cancers may be susceptible of reversion to the normal state, if we only understood the mechanism of differentiation. Unravelling this mystery could have profound implications for an understanding of cancer.

The history of recent advances in chemotherapy justifies extensive screening programs to find new and better anticancer drugs. It is not really necessary to know how a drug acts before we use it, as witness penicillin and introduction of antifolates. We knew that penicillin killed organisms before we knew that it prevented cell-wall synthesis by the bacterium. The antifolates followed Farber's astute recognition that folic acid caused leukemia to accelerate its progress.

When all this has been said we must recognize that the chemotherapeutic approach to cancer cure has been disappointing in its yield of useful drugs. Clearly we should have a chemotherapeutic agent that inhibits tumor growth before host toxicity occurs. For this we would have to know more about how these drugs exert their anti-tumor effect in a selective fashion, then perhaps we could exploit present agents better and design more effective ones. Finally there is the need to understand better the phenomenon of drug resistance and even combining drug therapy and varying schedules of drug administration.

When we consider the present state of cancer therapy and cancer research we recognize that empirical research of high quality is essential. At the same time we need to know far more about normal and abnormal cellular mechanisms. Only then can we hope to conquer this dread disease. The amount of basic information yet to be acquired is enormous and until we do this universal cancer control will not be available and until we do, it seems senseless to engage in indiscriminate cancer-cure crash programs.

L.H.N.

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175th ANNUAL MEETING

# of the

CONNECTICUT STATE MEDICAL SOCIETY

Hartford-Hilton Hotel

10 Ford Street, Hartford, Connecticut

April 25, 26, 27, 1967

PROGRAM COMMITTEE

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PRELIMINARY PROGRAM

Tuesday, April 25

Terrace Room

ANNUAL MEETING OF THE HOUSE OF DELEGATES

Kenneth F. Brandon, *Hartford, Speaker of the House, presiding*

8:30 Registration
Continental Breakfast for Delegates

9:00 Call to Order
Opening Session

11:30 Recess for Reference Committee Meetings

1:00 Luncheon

2:30 Final Session

6:00 Reception

what
time
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reported for every
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it's time
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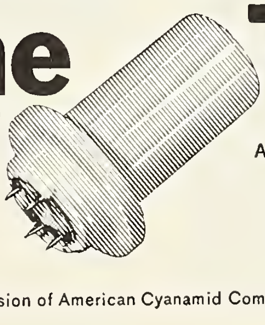

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Treatment Of The Rheumatoid Hand: Metacarpo-Phalangeal Joints*

James A. Albright, M.D. and Donald A. Nagel, M.D.

■ Surgery of the rheumatoid hand is a valuable adjunct in the total care of the rheumatoid patient. This paper will discuss the metacarpo-phalangeal joints, concentrating on treatment in later stages after subluxation or dislocation has occurred.

Etiology And Course

The course of the disease in the metacarpo-phalangeal joints is similar to other joints. Initially, an inflammatory synovitis occurs with pain, loss of motion and weakness, but without anatomical deformity. If inflammation persists, the collateral ligaments and capsule are slowly destroyed by the rheumatoid granulations, allowing deformities to occur.

Although rheumatoid infiltrations have been found in muscles, there is no good evidence that abnormal muscle activity is responsible for the deformities. In fact, preliminary evidence from EMG studies indicates that muscle activity is normal, which suggests that muscle abnormalities are secondary to the deformities and not responsible for them.[1]

Smith and Juvinal have recently presented a theory based on free-body analysis which relates the deformity to the long flexor tendons (flexor digitorum superficialis and flexor digitorum profundus).[2] During pinch these tendons carry a force almost three times (3F) the total force of the intrinsic muscles and six times (6F) the pinch force (F) at the finger-tip, which results in a force of 3F tending to subluxate the proximal phalanx anteriorly. The primary structures resisting this force are the collateral ligaments, and if these ligaments are weakened, the normal forces exerted by the flexor tendons will result in deformity, The flexor tendons may also be responsible for ulnar devia-

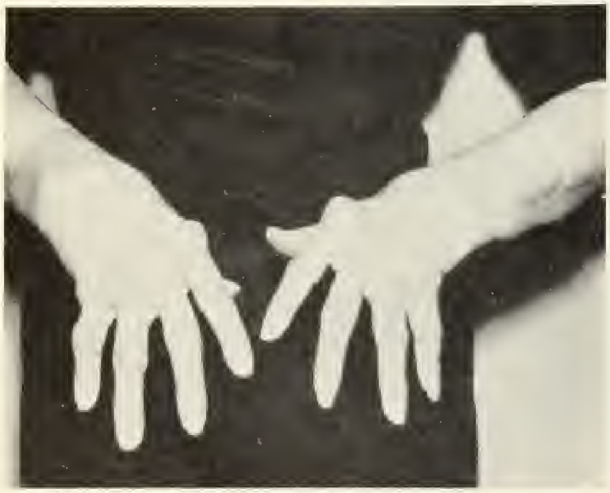

Figure Ia.
Severe rheumatoid deformities of both hands.

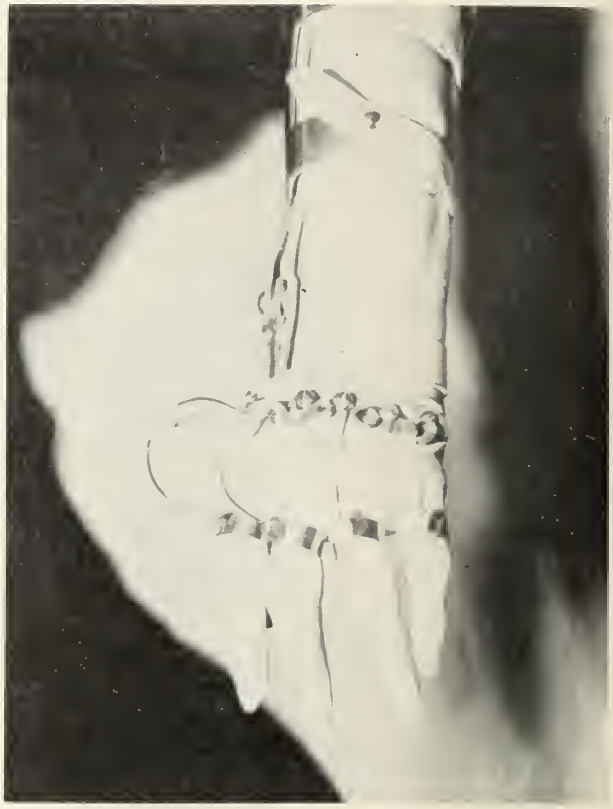

Figure Ib.
Left hand in splint. Because of improved function when wearing splints, the patient uses them routinely. Permanent improvement should not be expected.

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* *Supported in part by Public Health Service grant TI AM 5416-03.*

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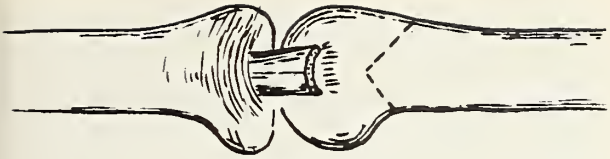

FIGURE IIa.

Lateral view of MP joint showing release of collateral ligament from the metacarpal, and the usual amount of bone removal.

tion since they angle ulnarward as they pass into the fingers (except in the little finger), producing a force tending to ulnar deviate the fingers.

Other etiological factors have been implicated and may be significant: Ulnar deviation of the long extensor tendons as they cross the metacarpo-phalangeal joints, contractures of soft tissues causing relative lengthening of bones, the force of gravity, and normal use of the hand which often produces an ulnar force against the fingers.

In addition to ulnar deviation and anterior dislocation of the proximal phalanges the extensor digitorum longus tendons displace ulnarward at the metacarpo-phalangeal joints, contractures of the intrinsic muscles on the ulnar side of the fingers develop, and hyperextension (swan-neck) deformities of the proximal-interphalangeal joints are accentuated by the anterior displacement of the proximal phalanges at the metacarpo-phalangeal joints.

Treatment

In the early stages steroid injections, splinting, and synovectomies may be useful. Once major deformities have developed, conservative treatment is less likely to be of benefit. However, even in this later stage, if the patient is cooperative, proper bracing can produce rather striking improvement in function. (Fig. I)

Significant improvement of the hand can often be attained with surgical treatment, and this is warranted if the total functional capacity of the patient can be increased. Surgery should provide adequate correction at the time of the initial operation since the final result is usually not as good if done in stages with multiple procedures.

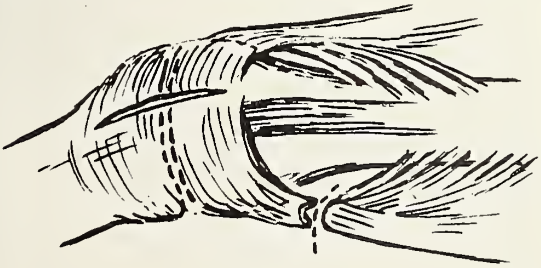

FIGURE IIb.

Dorsal view of ulnar deviation deformity. The initial incision in the hood is made on the radial side of the long extensor tendon and the intrinsic tendons are sectioned on the ulnar side of the finger only.

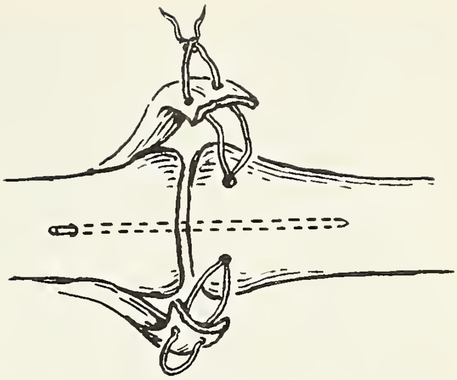

FIGURE IIc.

Dorsal view of the preferred method of stabilizing the joint. The collateral ligaments can be fixed securely using a single drill hole on either side of the metacarpal and a K-wire is used to fix the joint in the position desired.

Prostheses, especially the Flatt Prosthesis,[3] provide good stability, but motion may be limited. Since both stability and adequate motion result from a well-performed arthroplasty, use of a prosthesis is generally not necessary.

As in surgery on the rheumatoid foot, probably the single most important technical point is adequate removal of bone, usually from the metacarpals. Since the bone is relatively lengthened due to the soft tissue contractures, some bone should be removed even in cases with only moderate involvement, or deformity is likely to recur.

Although numerous procedures have been described and will give satisfactory results, careful at-

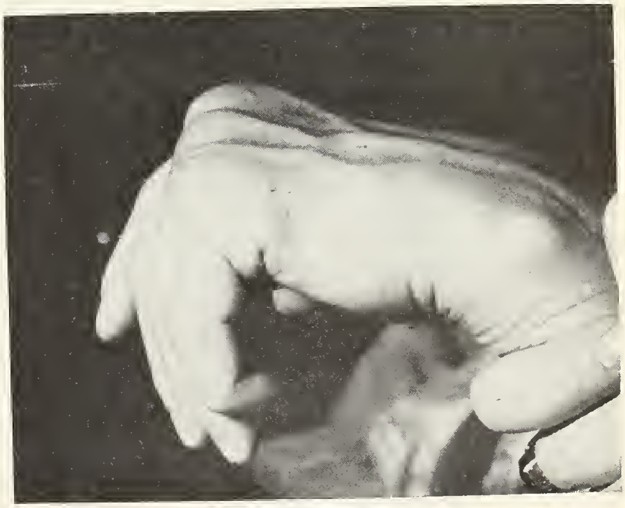

FIGURE IIIa

J.W. Preoperative

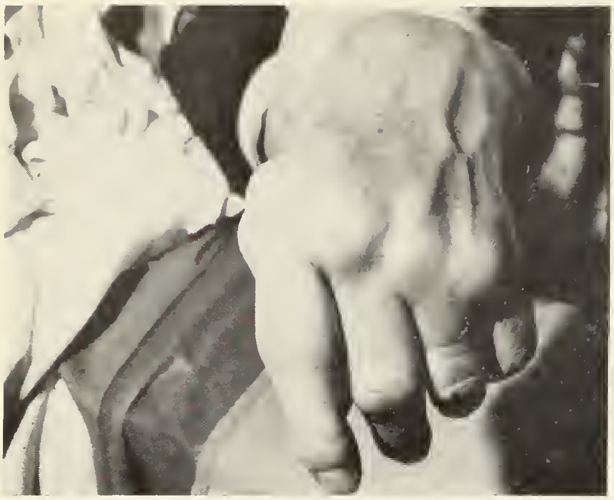

Figure IIIb
J.W. Preoperative

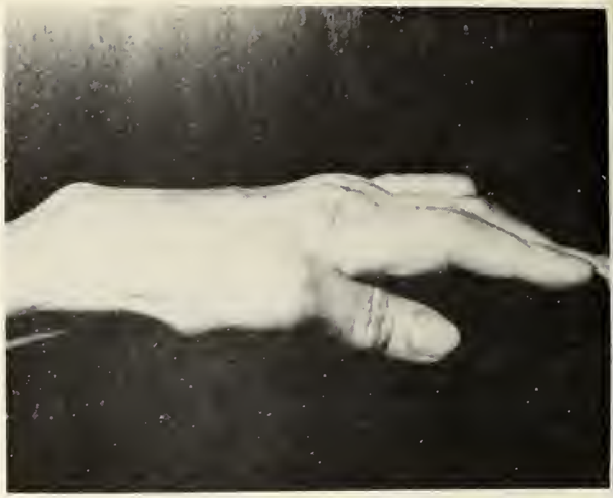

Figure IIId
Postoperative

tention to details of the particular technique being used is essential. The surgical plan should include:

1. Synovectomy
2. Shortening of metacarpals.
3. Provision of stability to proximal phalanx at MP joint.
4. Release of tight ulnar intrinsic tendons.
5. Repositioning of extensor tendons.
6. Protection of repaired structures post-operatively.

Technique

A transverse incision is made across the dorsum of the hand just proximal to the metacarpophalangeal joints (S-shaped incisions for each finger are used if surgery is to include the proximal interphalangeal joints). The dorsal veins and nerves lie in the fossa between the metacarpals and are preserved. To enter the joint, a longitudinal incision is made in the extensor mechanism on the radial

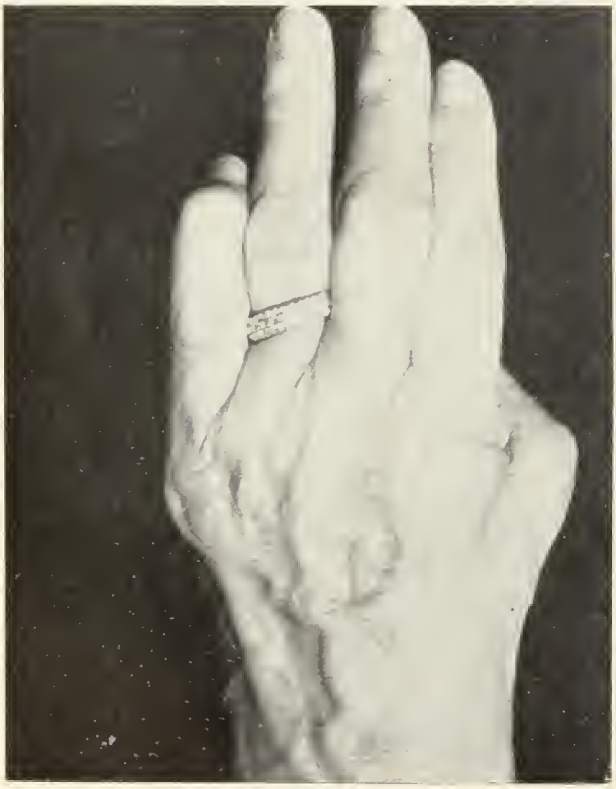

Figure IIIc
Postoperative

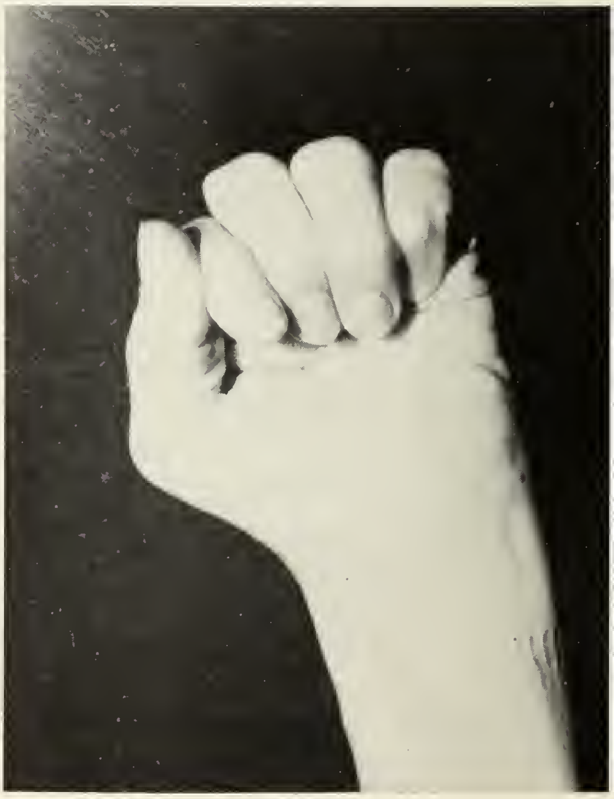

Figure IIIe
Postoperative

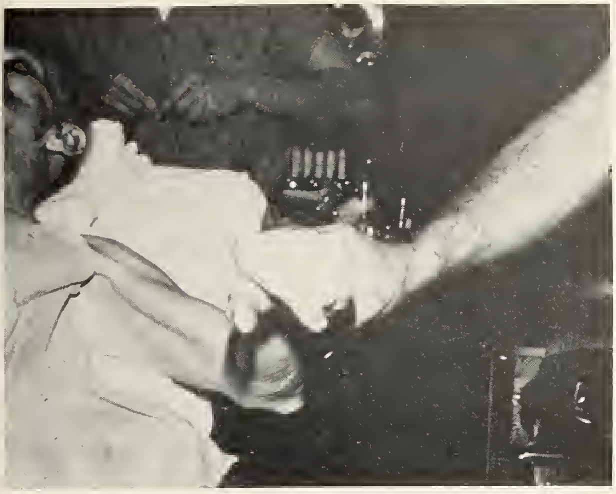

Figure IVa
C.O. Preoperative-Maximum extension seen in A-P view.

side of the extensor tendon, which will usually be dislocated ulnarward. If hypertrophic synovium is present, a partial synovectomy may be performed initially. Frequently, however, only a minimal or moderate amount of synovial tissue is present, in which case it is more expeditious to procede directly with the repair, excising any remaining synovium later in the procedure. After releasing the collateral ligaments from their insertions on the metacarpal, bone is removed from the metacarpal until the soft tissues are loose when the proximal phalanx is held in a reduced position. (Fig. IIa) Insufficient removal of bone is a more common error than excess removal. An attempt can be made to fashion the end of the metacarpal into a curved articular surface, but undue time should not be spent on this point. The intrinsic muscles to the ulnar side of the fingers are identified and their tendons sectioned, including the hypothenar muscles to the little finger. (Fig. IIb) They are found immediately dorsal to the deep intermetacarpal ligaments. Post-operatively, the muscles will regain continuity and will function in a lengthened position. Any remaining synovial tissue can be easily seen and is removed at this point.

Stability of the joint must be provided next, either by fixing the long extensor tendon to the base of the proximal phalanx or by reattaching the collateral ligaments to the metacarpal (theoretically better, since the flexor sheaths are pulled into a more normal position). The ligaments are attached to the metacarpal thru a single drill hole. A suture is first passed thru one ligament, then both ends of the suture are passed thru the metacarpal, thru the other collateral ligament and tied. (Fig. IIc) The finger is fixed with a Kirschner wire in full, or almost full, extension with slight radial deviation, and proper rotation. If the wire is inserted along the longitudinal axis of the finger, adjustments for improper rotation can be made easily. The extensor tendon is repositioned using either an overlapping technique or, if an ulnar relaxing incision in the hood has been necessary, the radial portion of the hood can be passed around the extensor tendon, suturing it to itself, which forms a sheath for the tendon. A muscle transfer providing for first dorsal interosseous function is not usually necessary. The wound is closed and a bulky compression dressing and splint are applied. When the dressing is applied, extreme care must be taken to position the fingers exactly, since the Kirschner wires do not provide completely rigid fixation. The wires are removed in 2-3 weeks and exercises started, using a splint part-time for protection.

Cases

J.W.: A 59 year old lady had a 30 year history of rheumatoid arthritis involving multiple joints, with typical deformities of the metacarpo-phalangeal joints of both

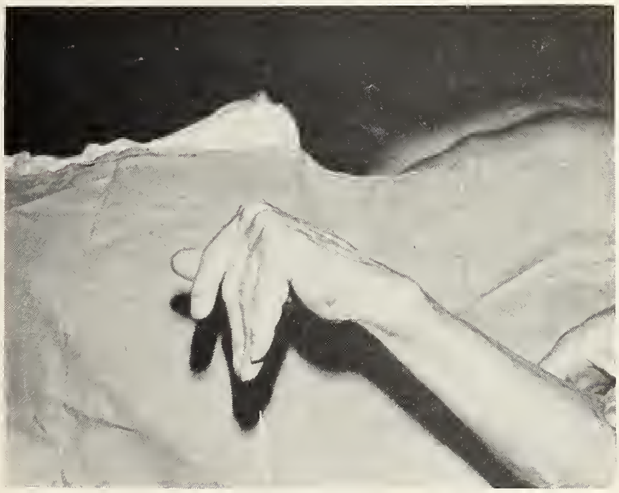

Figure IVb
C.O. Preoperative-Maximum extension seen in lateral view.

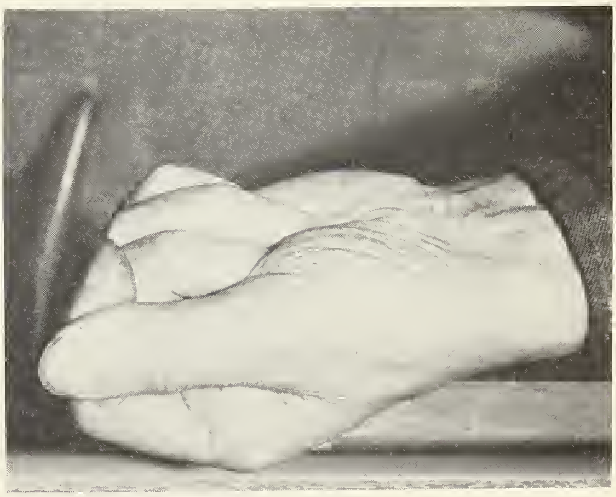

Figure IVc
Postoperative

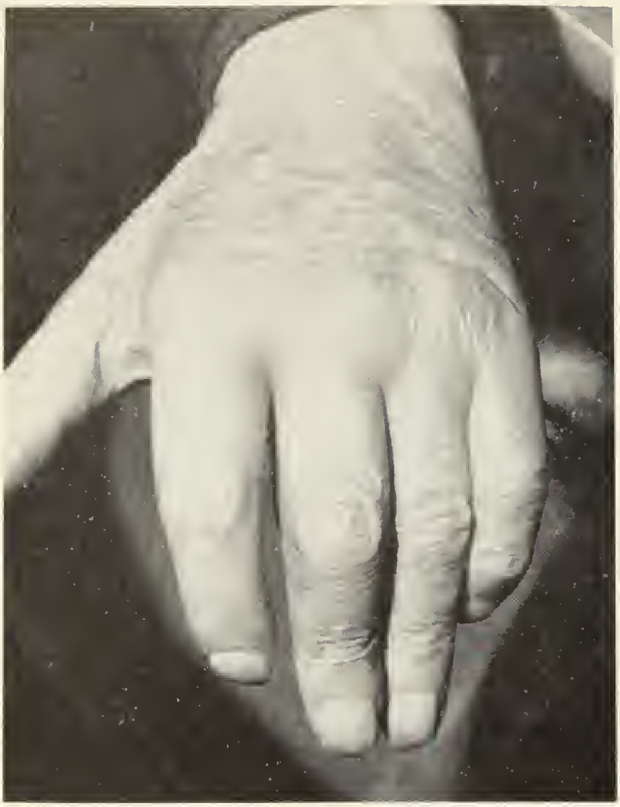

Figure IVd
Postoperative

hands. (Fig. III, a and b) On March 29, 1965, surgery was performed on the left hand which was the more severely involved. The above described technique was used, providing stability to the joints by suturing the extensor tendon to the base of the proximal phalanx through a drill hole. One year post-operatively the correction had been maintained and active metacarpo-phalangeal motion was good (full extension and 60° of flexion in all fingers, except the ring finger which lacked 5° of full extension). (Fig. III, c, d and e) Pre-operatively, the left hand had been the weaker hand, but since surgery it has been stronger and more useful than the right.

C.O.: A 59 year old draftsman had a ten year history of rheumatoid arthritis primarily involving the metacarpo-phalangeal joints of his hands, worse on the left. (Fig. IV, a and b) Although the left hand was dominant, it had become almost totally disabled because of severe flexion contractures of the metacarpo-phalangeal joints (due mainly to tight intrinsics). Neither active nor passive extension was possible at these joints, although the inter-phalangeal joints were almost normal. On March 8, 1965, arthroplasties were performed on the metacarpo-phalangeal joints of the left hand, providing stability to the joints by suturing the collateral ligaments to the metacarpals. Post-operatively, he gained full motion, except for some limitation of flexion of the metacarpo-phalangeal joint of the index finger, and he has had good use of the hand in his work. (Fig. IV, c and d)

Summary

Inflammatory rheumatoid granulations will weaken and destroy the joint capsule and ligaments over a period of time, and if the metacarpo-phalangeal joints of the hand are not protected by splinting, deformities will occur. These deformities limit the usefulness of the hand and should be corrected. The operative technique we have found most useful in bringing about correction is herin described in detail and illustrated with two cases.

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3. Flatt, A. E.: The care of the rheumatoid hand, C. V. Mosby Co., St. Louis, 1963.

PATIENT PERSONALITIES

One patient may have a sense of pride or a feeling of superiority because he knows that he is able to diagnose his own illness; he is merely allowing you to confirm this intuitive knowledge. Another will insist that the last thing he did or what he ate at that party is responsible for the symptoms. Don't bother to argue the point; evaluate the evidence and proceed. With tack and "tests" you may be able to change his mind.—H. U. Hopkins, M.D., Ed., *Leopold's Principles and Methods of Physical Diagnosis. Third Edition.* 1965, p. 3.

Cancer Of The Middle Esophagus Between Two Traction Diverticula

Case Report

N. William Wawro, M.D. and R. L. Painter, M.D.

■ Epidermoid carcinoma of the esophagus has been reported in association with pulsion diverticula of the esophagus and pharynx, but no instance of carcinoma associated with traction diverticula appears in the literature.

Traction diverticula of the esophagus, although not rare, are rarely symptomatic. The symptoms which do occur are related to their complications; bleeding, perforation with mediastinitis or spontaneous broncho-esophageal fistula, and conversion to a pulsion type with the symptoms of pulsion diverticula.[6] When these symptoms and findings appear in the patient with a traction diverticulum, investigation should be instituted to exclude these complications or that of carcinoma such as is described in the case report below.

Case Report

A 70 year old white woman was entirely well until six weeks prior to admission when she noted dysphagia to solid foods. She experienced substernal pressure with meals, particularly following the ingestion of solids and lost 15 pounds during her present illness, but experienced no difficulty swallowing liquids until the day of admission when she developed severe substernal pain after ingesting broth.

Her review of systems was non-contributory except for a family history of tuberculosis.

Physical examination revealed no abnormalities in this alert, elderly white female except evidence of recent weight loss. Her lungs, though somewhat emphysematous, were clear to auscultation and percussion. Her abdomen revealed no evidence of liver enlargement and was otherwise normal.

The results of her routine laboratory examinations were within normal limits. Blood type was O positive. X-rays of her chest revealed emphysematous lung fields with a few hilar node calcifications on the right and some tortuosity of the aorta. A barium swallow revealed two traction diverticula in the mid-third of the esophagus projecting to the right and measuring 15 mm. in diameter (See Figs. I and II.) The upper diverticulum was at the level of the tracheal carina and the lower one was 3 cm. below it was irregular esophageal narrowing between the two. Also noted were diverticula of the cardia of the stomach, the duodenum near the ampulla of Vater, and of the jejeunum at the ligament of Treitz.

At esophagoscopy the mobile esophagus contained an upper diverticulum which was directed antero-laterally from the right wall of the esophagus and had a smooth orifice with no evidence of inflammation of neoplasm. One centimeter distal to this was marked esophageal narrowing with an irregular mucosal lesion on the left postero-lateral wall, which became more extensive distally, encircling the esophagus and preventing further passage of the esophagoscope. A biopsy of this lesion revealed epidermoid carcinoma of the esophagus. Bronchoscopy was within normal limits.

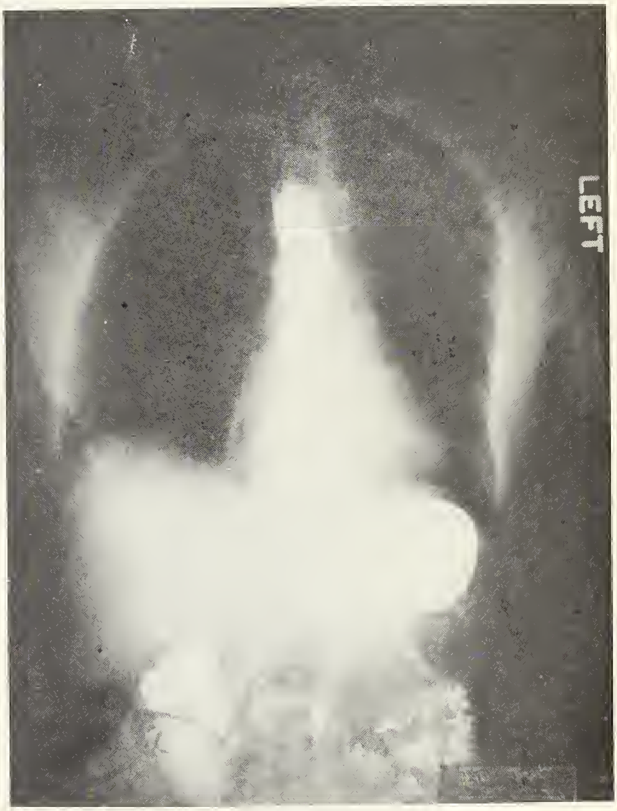

FIGURE I

Preoperative roentgengram revealing the mid-esophageal narrowing between two esophageal diverticula.

A resection of eighty per cent of the esophagus through a right postero-lateral thoracotomy incision was done on May 13, 1964. Through a separate upper abdominal midline incision the stomach was freed from all its vascular-areolar

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DR. R. L. PAINTER, Captain, United States Air Force Medical Department, Robbin's Field, Georgia.

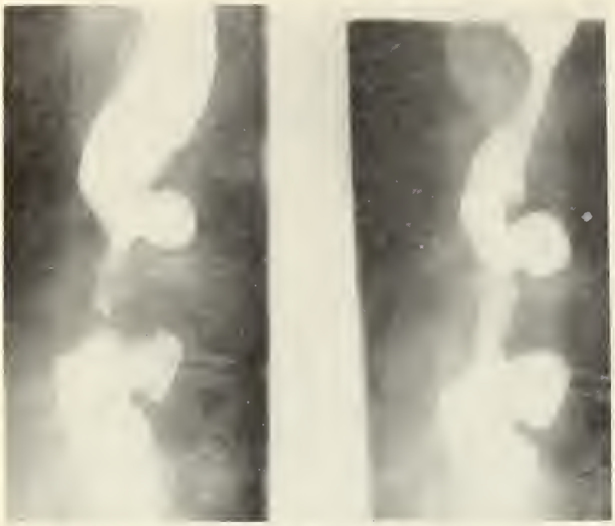

Figure II

Closeup view of X-ray indicating esophageal narrowing between two diverticula.

attachments, preserving only the right gastric artery and was drawn into the upper chest where a high intrathoracic esophagogastrostomy at the third rib level was performed utilizing a two layer interrupted silk anastomosis. (See Fig. III.) A pyloromyotomy was done.

Pathological examination of the esophagus showed a three centimeter diameter, ulcerating lesion located between but not involving either of the two diverticula. There was no evidence of local extension of the tumor. Microscopic examination showed a Grade II epidermoid carcinoma of the esophagus with no lymph node metastases. (See Fig. IV) The proximal margin was six centimeters from the lesion and was free of cancer. The distal margin was also uninvolved by tumor.

She made an uneventful recovery except for a brief period of hypochloremia and hyponatremia and was discharged on the sixteenth postoperative day eating a six-feeding ulcer bland, high protein diet. She continued to do well until August, 1964 when dysphagia recurred. She was re-admitted, esophagoscoped, and an ulceration on the posterior wall of the anastomosis was biopsied, revealing recurrent epidermoid carcinoma. (See Fig. V)

6065 gama Roentgens of Cobalt therapy were given through two 8 x 5 centimeter portals over a fifty-two day period. Some symptomatic improvement followed, but dysphagia returned and the patient died of her disease in a nursing home in May, 1965. An autopsy, performed several hours after death, revealed recurrent epidermoid cancer at the site of the intra-thoracic esophago-gastric anastomosis, with an associated tracheo-esophageal fistula and metastatic carcinoma of the liver.

Discussion

Without differentiating between pulsion and traction diverticula, Bockus[2] writes that carcinoma may occur in as many as 10 per cent of patients with esophageal diverticula. Hoover,[4] in 1945, reported the Lahey Clinic experience of esophageal diverticula noting an incidence of carcinoma of 1.08 per cent. This is much larger than the incidence of carcinoma of the esophagus in the general population as found by Steiner[7] who examined 9000 consecutive autopsies in order to determine the origins of esophageal cancer. He found eight, small clinically silent squamous cell carcinomas. This is an incidence of less than 0.1 per cent. In none of

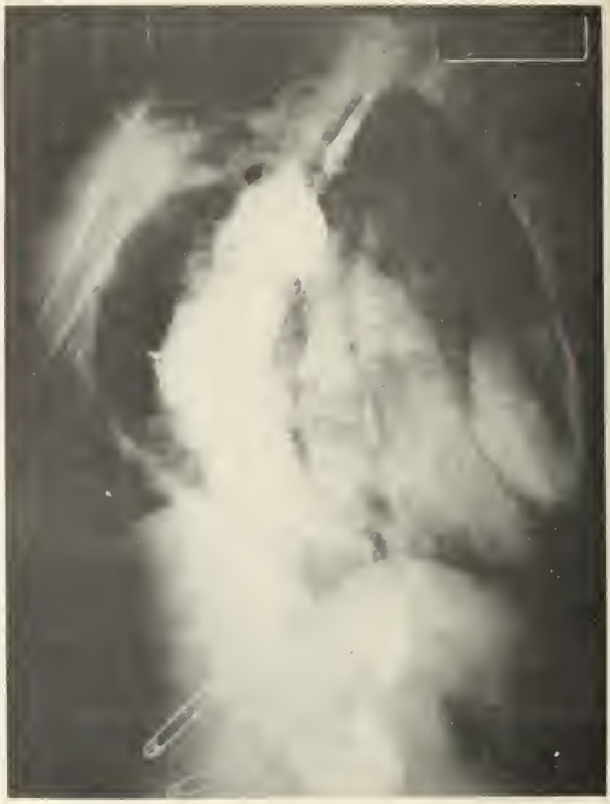

Figure III

X-ray study of high intra-thoracic anastomosis on twelfth postoperative day.

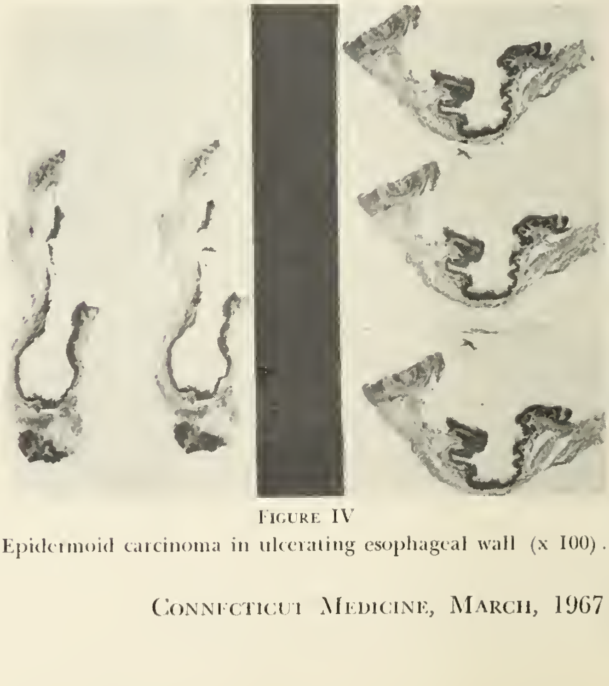

Figure IV

Epidermoid carcinoma in ulcerating esophageal wall (x 100).

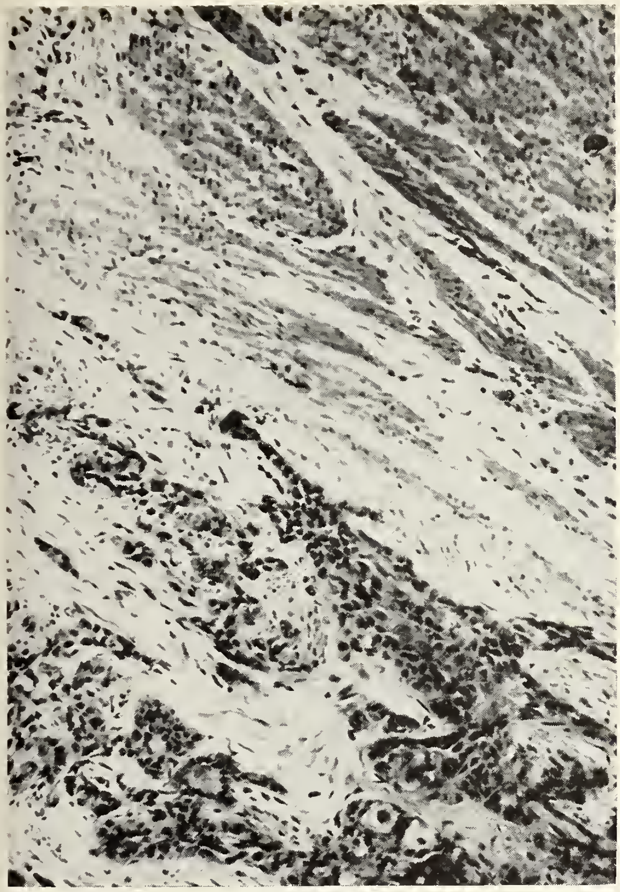

FIGURE V

Biopsy of esophago-gastric anastomosis indicating recurrent squamous carcinoma (x 450).

these carcinomas was there an associated diverticulum of any type.

Riberi is credited with reporting the first carcinoma in a pharyngo-esphageal diverticulum.[5] In 1961, Garlock and Richter,[3] following a review of the literature, found twenty such cases, only twelve of which they felt fully met the criteria for *de novo* carcinoma arising in the pulsion diverticulum.

The occurrence of food stasis in the large cervical pulsion diverticula has been thought to be the source of chronic irritation which leads to metaplasia and then sequentially may develop into carcinoma. An increased incidence (1.5 per cent)[4] of carcinoma of the esophagus in the dilated proximal segment of patients with achalasia seems to support such an hypothesis. Other types of chronic irritation have been associated with an increased incidence of carcinoma of the esophagus, such as lye stricture and the large intake of hot drinks and alcohol. In addition, leukoplakia, due to chronic inflammation is associated with carcinoma of the esophagus in two-thirds of patients reported by Schaer who is quoted by Steiner.[7]

No author, however, reports carcinoma of the esophagus in association with traction diverticula. Since traction diverticula are seldom associated with stricture, stasis or obstruction, this fact should not be unexpected. One case of traction diverticulum reported by Adams[1] progressed to stricture severe enough to require resection, but there was no associated carcinoma.

Unlike the pulsion diverticulum, the traction diverticulum is formed by an extra-esophageal, inflammatory process which preserves the full thickness of the esophageal wall. (See Fig.VI.) Fluoroscopic studies[8] show that traction diverticula empty by contracting and that they fill only by back pressure. This means the traction diverticulum is empty of food and debris except while the patient is actually swallowing and is not subjected to the chronic irritation of fermenting food.

In the patient described above, carcinoma was found located between two traction diverticula, but not involving or arising from them. The symptoms of obstruction and the finding of an irregular esophageal narrowing in this area by X-ray led to esophagoscopy and the correct diagnosis. There was no evidence of narrowing at the distal diverticulum and no stasis, so the combination of the two

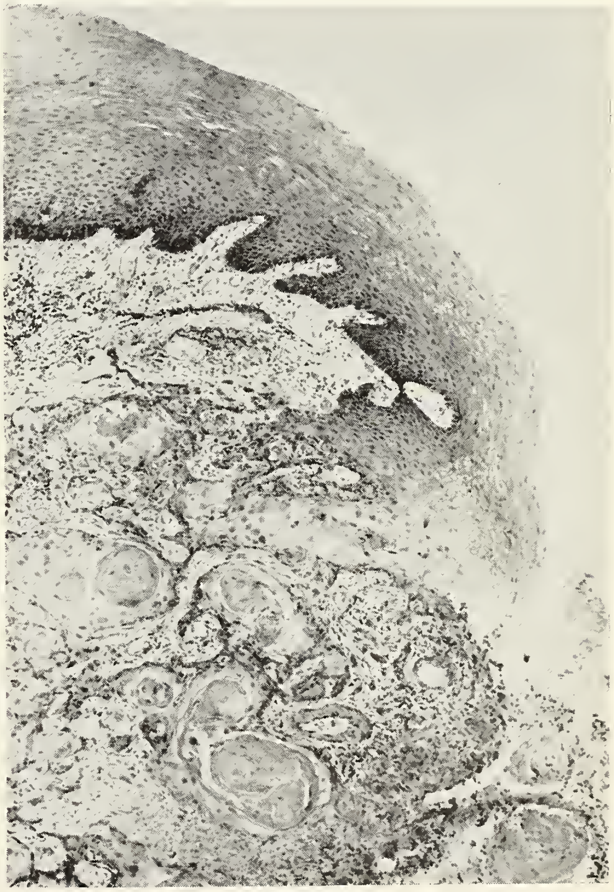

FIGURE VI

Photomicrograph of esophageal wall including upper and lower diverticulae, demonstrating the full thickness of the esophageal wall, i.e., mucosa and muscularis. (x 3) lesions must be considered a coincidence. One wonders that the two lesions have not been reported in conjunction with one another previously since the mid-esophagus is the sole location for traction diverticula and the most common site for squamous cell carcinoma of the esophagus.

Summary

A case of squamous cell carcinoma of the mid-esophagus in association with two traction diverticula is reported. A review of the literature fails to reveal any similar case.

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IMPORTANT NOTICE

Reference Committee Hearings Scheduled

April 25-27

A major procedural change has been made for the Annual Meeting of the House of Delegates, scheduled for April 25-27 at the Hartford-Hilton Hotel. For the first time, all reports of officers and division chairmen, as well as all resolutions introduced by individual members or county associations, will be sent to Reference Committees for hearing, study, and report.

This new method of conducting the business of the House will give all members of the Society, as well as delegates, the opportunity to attend the Reference Committee hearings and express themselves on reports or resolutions under consideration.

County association resolutions should be submitted to the Office of the General Manager as soon as possible so that they may be duplicated and distributed to the Delegates. Through such expression of "grass roots" thinking the Society will be able to share and act on matters of professional concern and build toward a stronger, more effective medical organization.

Percutaneous Transhepatic Cholangiography In The Diagnosis Of Jaundice

Joseph P. Dineen, M.D., Theodore Ditchek, M.D. and Gerald T. Scanlon, M.D.

In 1937, many years before the fall of Dienbienphu and the Geneva Treaty which partitioned Southeast Asia, Huard and Do-Xuan-Hop[10] reported in the Bulletin de la Societe Medico-Chirurgicale de l'Indochine two cases in which they obtained cholangiograms by injecting Lipiodol percutaneously into the intrahepatic bile ducts. Because the world was concerned with graver problems then and in the following years, no notice was made of this report. Earlier, in 1921, Burckhardt and Müller[3] were able to obtain quite good cholecystograms and cholangiograms by the percutaneous injection of the gall bladder in cadavers and several patients. This procedure was further utilized by Lee[13] in 1942 with the aid of the peritoneoscope. However, it was not until 1952 that Carter and Saypol[4] rediscovered percutaneous transhepatic cholangiography and their case report awakened interest in the technique in this country. Since then, the examination has gained scattered enthusiasm and its usefulness has not been completely appreciated in all areas. In order to gain more widespread and greater acceptance of this procedure, we are submitting this report to include our first seven studies.

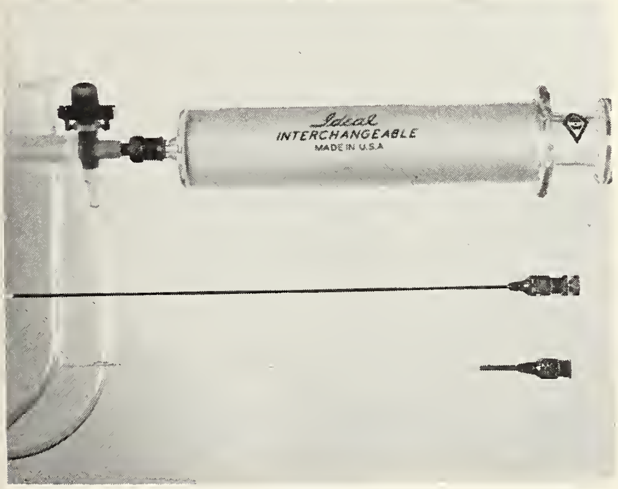

FIGURE I

The No. 18 teflon catheter with its No. 19 guage stylet is demonstrated.

From the Departments of Surgery and Radiology, Veterans Administration Hospital, West Haven, Connecticut; and Yale University School of Medicine.

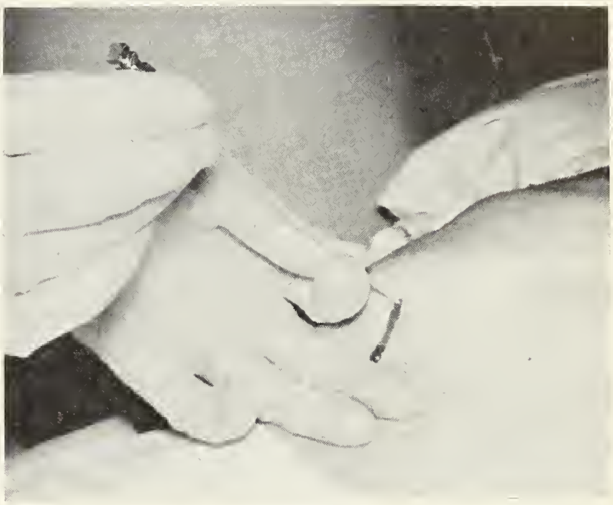

FIGURE II

After local infiltration with 1% xylocaine, a small skin incision is made and the teflon catheter with its stylet in place is introduced in the mid-clavicular line.

Technique

The patient, having fasted for eight hours, is examined in the X-ray department according to the method described by Evans et al.[6] A No. 18 teflon catheter with a No. 19 stylet is used (Fig.I). Puncture is made anteriorly, just under the right costal margin in the mid-clavicular line (Figs. II and III). Prior fluoroscopy with a long intestinal tube placed in the duodenum may be used as a guide for selection of the puncture site.[7] 50 per cent Hypaque is injected either after aspirating bile (Fig. IV), or by confirming placement in a biliary duct by the injection of small quantities of radiopaque medium utilizing the fluoroscope and image intensifier (Fig. V). As much dye as is necessary to adequately fill the biliary tree is injected. Exposures are made supine, in multiple projections, and upright if necessary. The contrast medium is either completely

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DR. GERALD T. SCANLON, Assistant Professor, Radiology, Yale University School of Medicine.

TABLE I
PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY
VETERANS ADMINISTRATION HOSPITAL, WEST HAVEN, CONNECTICUT

PATIENT	AGE	SEX	DIAGNOSIS	PTC	RESULT	TREATMENT	RESULT
1. J.W.	68	M	Metastatic carcinoma rectosigmoid	2/1/65	Non-visualization	Exploration Liver biopsy	Expired
2. S.S.	71	M	Carcinoma pancreas; Oat cell carcinoma, lung	4/22/65	Successful study	Cholecysto-jejunostomy	Improved Expired 4 mos. later of carcinomatosis
3. E.S.	45	M	Bile duct carcinoma	5/27/65	Successful study	Exploration Hepatotomy	Expired
4. A.S.	41	M	Choledocholithiasis	3/9/66	Non-visualization	Cholecystectomy Choledocholithotomy	Improved
5. G.L.	77	M	Choledocholithiasis	3/25/66	Non-visualization	Cholecystostomy	Improved
6. J.C.	76	M	Choledocholithiasis	3/29/66	Successful study	Cholecystectomy Choledocholithotomy	Improved
7. C.T.	54	M	Bile duct carcinoma	5/27/66	Successful study	Modified Longmire procedure	Expired 2 weeks later liver failure

aspirated at once or the catheter left in place at the completion of the procedure for decompression and drainage.

Clinical Material

As noted in Table I, seven patients have been studied during the past 14 months at the West Haven Veterans Administration Hospital. Our first patient developed jaundice, acholic stools and dark urine while nearing completion of X-ray therapy for local recurrence of a carcinoma of the rectosigmoid. The liver chemistries were obstructive in type. Metastatic disease to the liver was suspected but could not be proven. The liver was not palpable and a liver scan was unremarkable. In addition, the patient had a past history of cholecystectomy and choledocholithotomy in 1962. Because we could not rule out a benign extrahepatic cause for his jaundice, he was subjected to percutaneous transhepatic cholangiography. When we were unable to demonstrate dilated intrahepatic bile ducts we suspected that he did not have extrahepatic biliary obstruction, but felt that a negative examination should not preclude exploration. At operation the left lobe of the liver was found to be replaced by tumor and the needle tract had passed through tumor tissue. The patient expired six days later of his underlying disease,

The second patient had proven oat cell carcinoma of the lung with cervical node metastases. He developed signs and symptoms of obstructive jaundice but was otherwise in good health. Because his prognosis was not certain after extensive X-ray therapy to his neoplastic lesion and the cause of his jaundice was not clear, he was subjected to percutaneous cholangiography. A picture (Fig.VI) of massive dilatation of the biliary tree and distal cut off of the common bile duct characteristic of the obstruction caused by carcinoma of the head of the pancreas was encountered. Free communication with the gall bladder was demonstrated and accordingly a cholecystojejunostomy was performed under local anaesthesia. The patient did quite well for four months with complete clearing of his jaundice. When he eventually succumbed to his pulmonary malignancy, a necropsy revealed a second primary malignancy in the head of the pancreas totally obstructing the distal common bile duct.

Our third patient had obstructive jaundice due to lesions in the intrahepatic bile ducts which were most probably bile duct carcinoma. A percutaneous cholangiogram was done to ascertain if a dilated channel was present that could be used for a Longmire procedure. It was possible to demonstrate a biliary radicle in the left lobe of the liver arising in the lateral segment. However, this was not dilated. Seven months later because of his progressive deterioration an exploration with hepatotomy was performed. It was impossible to benefit the patient and he expired postoperatively. Permission for postmortem examination was not obtained.

Our next three cases had obstruction due to common duct stones but as in the earlier cases, the diagnosis could not be made preoperatively by any of the usual methods including intravenous cholangiography because the serum bilirubins were too

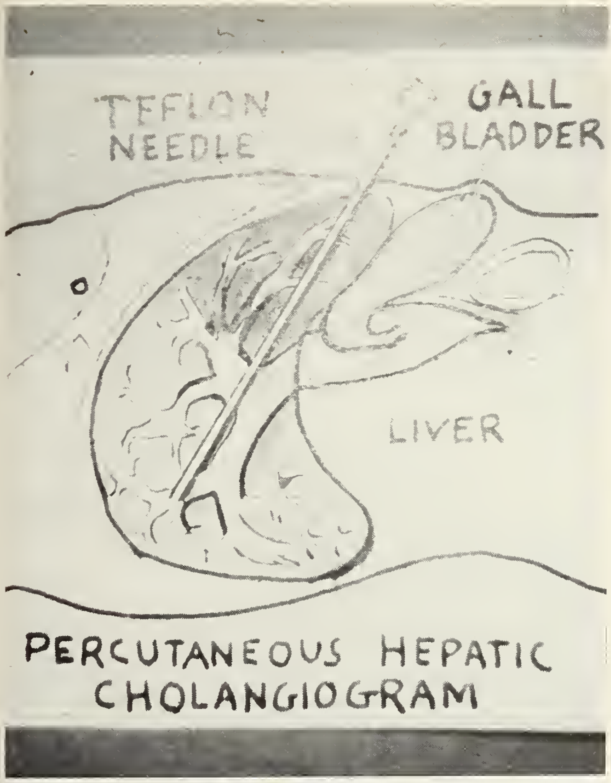

FIGURE III

Diagramatic representation of the course and depth of the catheter insertion. After removing the stylet, the catheter is slowly withdrawn until a biliary radicle is entered.

elevated. Due to technical difficulties we were unable to visualize the intrahepatic ductal system in patients 4 and 5. In case 6, the patient was quite an elderly gentleman and a diagnisis of malignant obstruction had been entertained. We were able to demonstrate quite nicely (Fig. VII) the true nature of the obstruction.

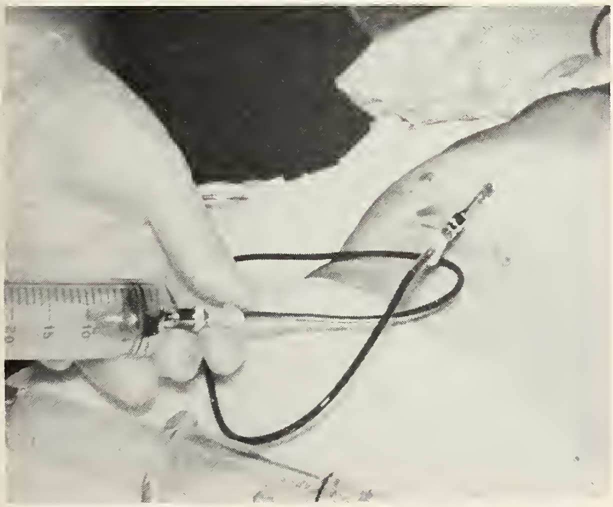

FIGURE IV

Dark bile under some pressure is being aspirated prior to injection of the contrast medium.

FIGURE V

Contrast is about to be injected under direct fluoroscopic control using the image intensifier.

Our latest case was that of a 54 year old male who developed jaundice, dark urine and light stools without abdominal pain while in the local jail. On admission in April 1966 his serum bilirubin was 38.0 mgms per cent with a direct fraction of 22.0 mgms per cent. A liver biopsy on May 13 revealed

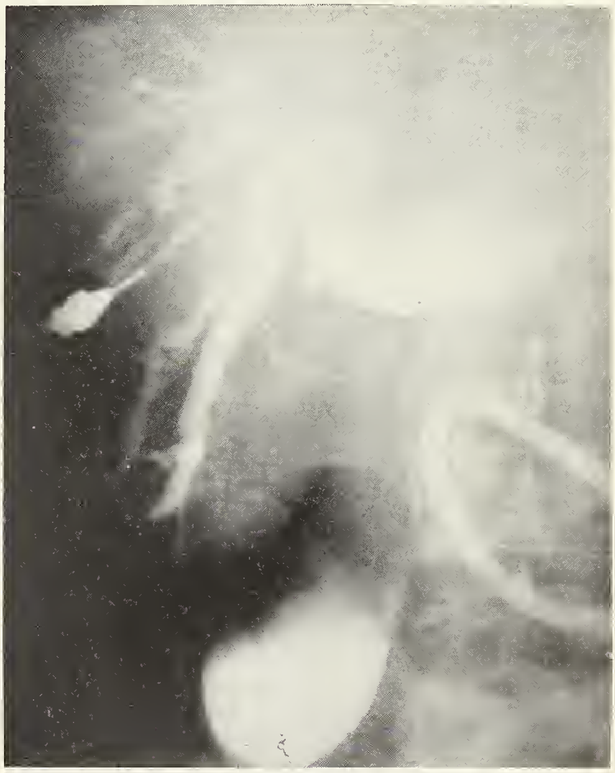

FIGURE VI

Case 2. There is massive dilatation of the biliary tree with a complete and sharp distal cut off. The gall bladder which was greatly dilated is partially filled in the lower portion of the picture. The teflon catheter is seen in place and the long intestinal tube outlines the duodenal sweep.

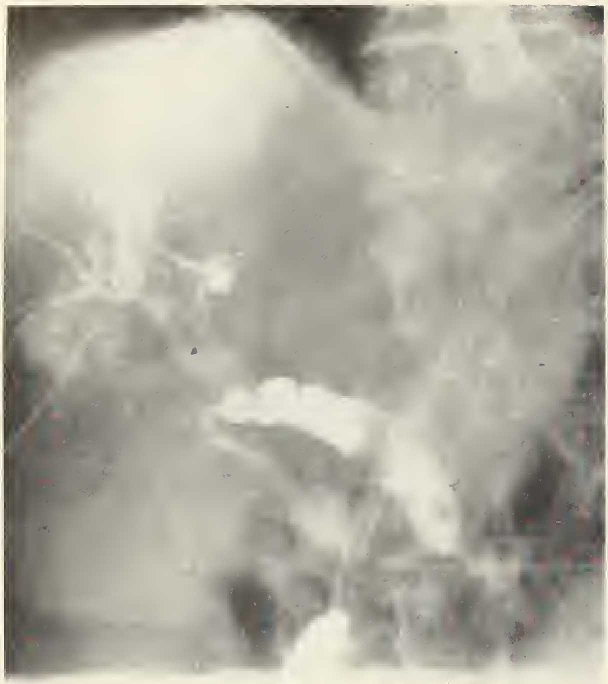

Figure VII

Case 6. The common bile duct is somewhat dilated and several radiolucent stones are apparent. The intrahepatic biliary radicles are not grossly dilated.

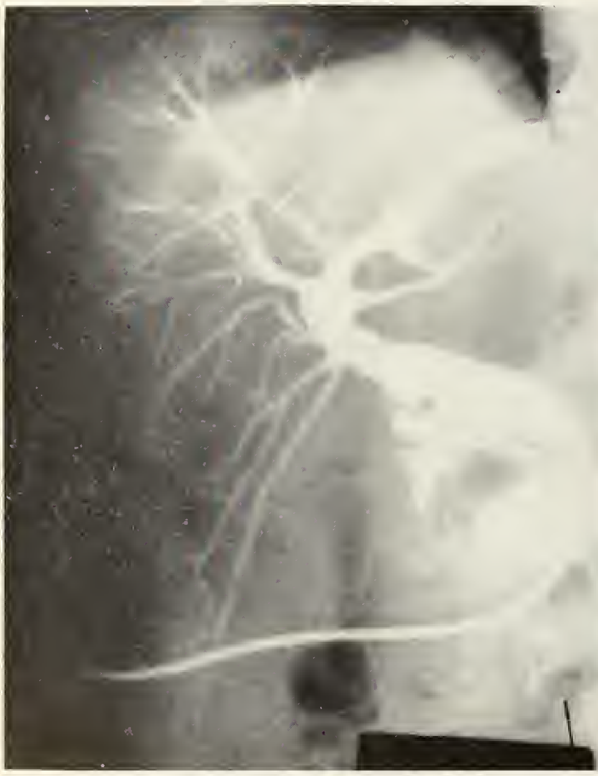

Figure VIII

The operative cholangiogram confirms the small caliber of the intrahepatic bile ducts.

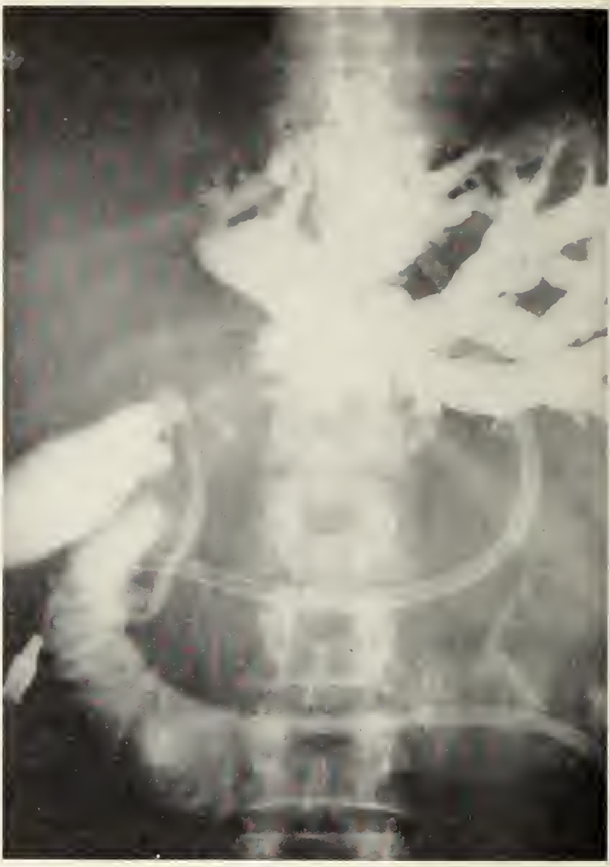

Figure IX

Case 7. Massive dilatation of the intrahepatic biliary radicles of the left lobe with normal common bile duct and gall bladder.

marked bile stasis and cirrhosis. A liver scan disclosed no localizing lesions. On May 27 a percutaneous puncture of the left lobe of the liver with cholangiography revealed massive dilatation of the biliary radicles in the left lobe with no visualization of the right side (Fig. IX). Magnification views disclosed an almost completely occluded proximal segment of left hepatic duct with involvement of the bifurcation (Fig. X). The common hepatic duct, gall bladder, cystic duct and common bile duct appeared normal. A puncture was then made of the right lobe of the liver and again massive dilatation of the intrahepatic biliary radicles was encountered with complete obstruction at the bifurcation of the common hepatic duct (Fig. XI). Both teflon catheters were left in place, the right side remaining open for three days and the left sided catheter functioning for two weeks. During this period of decompression the serum bilirubin fell to 8.4 mgms per cent and the patient was prepared for surgery. The preoperative diagnosis on the basis of the cholangiography was bile duct carcinoma. On June 16 a modified Longmire procedure was carried out with anastamosis of a Roux-Y loop of jejunum to a dilate intrahepatic channel in the left lobe of the

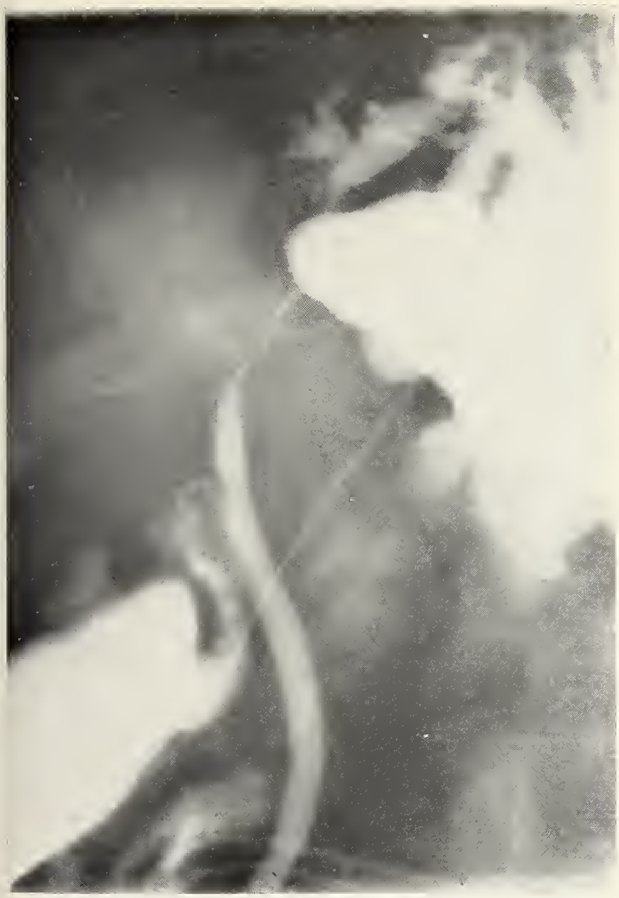

Figure X

Case 7. Image intensification reveals almost complete obstruction of the proximal portion of the left hepatic duct from the bifurcation.

dilated liver. Unfortunately the patient succumbed two weeks postoperatively of intractable liver failure. At postmortem examination the anastamosis was patent and there was no evidence of leakage. The microscopic sections confirmed a diagnosis of bile duct carcinoma in a lesion measuring 4.5 by 3.5 centimeters in diameter, arising at the bifurcation of the common hepatic duct. There were no extra-hepatic metastases.

Discussion

The differential diagnosis of jaundice can frequently be quite challenging. In a relatively small but appreciable percentage of cases, a definitive diagnosis as to the etiology of the jaundice cannot be established despite utilization of all available laboratory tests, liver biopsy and the standard radiologic techniques. Frey and Glenn[8] have reported on 19 cases of jaundice due to either impaired glucuronide metabolism, such as Gilbert's disease, or due to excessive hemolysis such as with Cooley's disease, sickle cell anemia, or congenital hemolytic anemia. In these conditions the hepatic excretory function is usually normal and the authors were able to obtain satisfactory oral cholecystograms or intravenous cholangiograms in 14 of these patients. Save for this type of problem, the standard radiologic studies will fail to visualize the ductal system if the serum bilirubin is 3.0 mgms per 100 ml. or above, and will only rarely visualize above 2.0 mgms/100 ml. Despite the use of intravenous drip cholangiograms, we were unable to visualize the biliary tree in any of our patients before percutaneous transhepatic injection.

The need for arriving at early diagnosis in cases of jaundice has been well documented by Aronsen.[2] In his experiments reported in 1961, he demonstrated early hepatocellular involvement in canines by a rise in the transaminase levels in the serum after only several days of complete biliary obstruction. He further found that if the obstruction were continued for a period of between 14 and 21 days, then bile flow restored, the liver was unable to regain completely its ability to eliminate intravenously administered I^{131} rose bengal, bromsulphalein, and galactose. This irreversibility was found to be due to impairment of the effective hepatic blood flow as measured by the colloidal radiogold study, and as confirmed by portal venography which

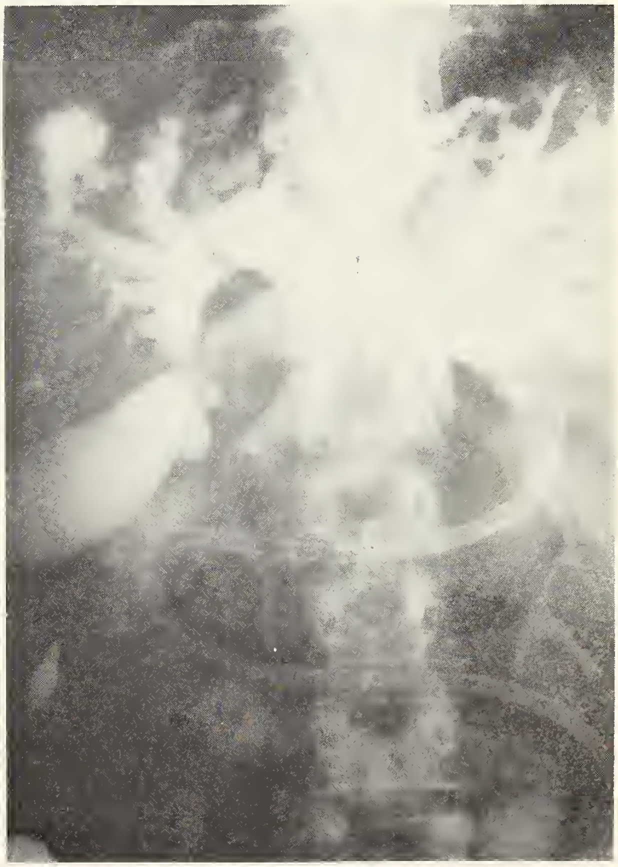

Figure XI

Case 7. Opacification separately of the right lobe reveals dilation of the intrahepatic bile ducts with block at the bifurcation of the common hepatic duct.

demonstrated a permanently altered intrahepatic vascular architecture, with a fair degree of portal-systemic venous shunting.

Many feel that the procedure is unnecessary and not worthwhile since the patient will be explored anyway. Yet, as Kaplan, Brodsky and Rumball[11] have well pointed out, it is advantageous and often essential to avoid anaesthesia and surgical trauma in patients with parenchymal liver disease. With the demonstration of an unobstructed biliary tree, the patient with hepatitis can be spared operation. The visualization of the normal biliary tree by this technique has been well demonstrated by Arner[1] who has successfully outlined 18 of 35 normal bile ducts with the aid of the image intensifier and television monitoring. Evans[5] visualized three of six normal ducts by the same method. In case 6 of the present series, the percutaneous cholangiogram (Fig. VII) and the operative cholangiogram (Fig. VIII) demonstrate the small caliber of the intrahepatic bile ducts that can be visualized by this technique. Where indicated, operation may then be avoided since the incidence of bile leakage or hemorrhage following the procedure is quite low, Evans[5] reporting one instance of each in his first 93 cases. In the cases comprising the present report there was no instance of hemorrhage or bile leak. The use of the flexible teflon catheter has without doubt lessened the chances of injury to the liver during these studies.

Wiechel,[15] Evans,[5] Glenn et al,[9] Kaplan et al,[12] and Shaldon et al[14] have all reported their experience with this procedure in the past several years. The X-ray appearance of the bile ducts and especially the characteristics of the distal cut off as described radiographically and illustrated by Evans[5] can in most instances provide a very accurate preoperative diagnosis. In additionthe same writer has found that this examination triples the number of positive preoperative diagnoses in carcinoma of the pancreas as compared to G. I. series, and almost doubles the diagnostic accuracy in carcinoma of the Ampulla of Vater.

It can be said that with proper selection of patients, by correction of any coagulation deficiencies prior to the examination, and by close attention to detail, this procedure can provide much useful information with a very low incidence of complications. However, although the relative percentage of complications is very low, they must always be anticipated. We do not perform this examination on any patient who is not a candidate for a surgical procedure under general anaesthesia, or on any patient whose medical status would contraindicate the possibility of major surgery. An operating room is always kept prepared for immediate laparotomy should signs of bile leakage or hemorrhage develop following the procedure. Even in those patients who are certain to be explored, unless a clear cut diagnosis and site of the lesion can be established by other means, this examination will be very helpful preoperatively and make any operative procedure better planned and more easily executed. It has been found especially useful in cases of postoperative stricture.

Summary

A report is submitted of an experience with seven patients undergoing percutaneous transhepatic cholangiography. Some of the pertinent history of this procedure and recent work have been discussed. It is hoped that a greater awareness of the availability and value of this technique will stimulate its greater use.

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Some Preliminary Data On The Postmastectomy Treatment Of Female Breast Cancer In Connecticut

Henry Eisenberg, M.D., M.P.H. and Roger R. Connelly, M.S.

■ The treatment approaches to the various stages of breast cancer have continuously been a source of discussion. The physician has to make an especially difficult decision when determining the therapy of advanced breast cancer cases. His final choice of treatment will depend upon a great number of different factors. The physician is primarily interested in saving the patient's life or prolonging it, i.e., he is interested in the quantity of survival. To best accomplish this goal of increasing the quantity of survival, the physician has been known, at times, to resort to quite radical or even supraradical therapeutic methods. His judgement is almost always based upon either his personal experience or upon reports published by responsible investigators. This report contains information on endocrine ablative procedures and other postmastectomy treatment methods employed in female breast cancer by the physicians in a circumscribed population during recent years, which permits statements as to the survival experience of the average breast cancer patient.

Material

The data to be presented were obtained from the Connecticut Tumor Registry, a repository of information on cancer diagnosed among all Connecticut residents. It is one of the largest and oldest Central Registries and the only one within the United States which is based on a total defined population. Since its beginning in 1935, all cases of cancer diagnosed in the state of Connecticut have been reported to the registry by the hospitals within the state. Follow-up is accomplished in 97 per cent of cases.

At present, the registry has approximately 150,000 cases of cancers on record and is following about 40,000 cases annually. Each year approximately 9,500 new cases are added to the roster. The information collected contains among other items the age and sex of the patient, the site and stage of the tumor, the date of diagnosis, and the various treatments given. If additional therapy was instituted after the patient is discharged, this information usually becomes available during follow-up observations.

Various statistical indices reflecting survival can be calculated using these data, for example, yearly survival rates. When a large number of cases are available, these rates can be made specific for numerous variables. Survival computed from these data are of special interest since they describe the survival experience of the "average" cancer patient treated by the "average" physician without the selection bias in data based upon cancer patients seen in specialized cancer hospitals or collected by cancer specialists.

Although the registry has data on patients diagnosed since 1935, information on endocrine ablative procedures has been routinely coded only since 1957. All female breast cancer patients diagnosed during the period 1957-62, with follow-up into 1964 have, therefore, been selected for analysis. Additional information for all cases treated by one medical oncologist in the state was made available to the authors and these cases were studied in depth, particularly with regard to date of recurrence and also to the additional hormonal and chemotherapeutic approaches used by this oncologist.

Results

A total of 5,198 women were diagnosed in Connecticut during the years 1957-62, as having breast cancer. Nine out of every 10 of these patients received radical or simple mastectomy as part of their primary treatment and the subsequent analyses are restricted to these 4,726 cases. Their age and stage distribution is shown in Table I.

In the registry system, the total treatment a patient receives is coded in two parts:

Presented at the International Symposium on the Major Endocrine Surgery and the Treatment of Advanced Breast Cancer in Lyon, France, May 1966.

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TABLE I

Distribution by age and stage of disease at diagnosis: Female breast cancer cases with radical or simple mastectomy as primary treatment, Connecticut, 1957-62.

	AGE AT DIAGNOSIS			
	LESS THAN 55 YEARS		55 YEARS OR OLDER	
STAGE OF DIAGNOSIS	NO.	%	NO.	%
Total cases	2195	100.0	2531	100.0
Localized	1060	48.3	1232	48.7
Regional	972	44.3	1020	40.3
Remote	74	3.4	100	4.0
Unknown	89	4.1	179	7.1

(a) First course of therapy—All therapy directed towards tumor tissue, whether for cure or palliation. To be included in the first course, treatment must be initiated within six months of the date of diagnosis. Medical hormone therapy is distinguished from endocrine surgery or radiation for hormonal effect. In some of the subsequent tables, those feamale breast cancer patients receiving endocrine surgery or radiation during the first course of therapy were all classified as "prophylactic castration" cases without further review. It is felt that the bias inherent in this arbitrary designation is small in magnitude.

(b) Subsequent therapy—All tumor directed therapy not considered part of the first course. Again, all patients receiving endocrine surgery or radiation as all or part of their subsequent therapy are arbitrarily classified as "therapeutic castration" cases.

Of the 4,726 patients with mastectomy as primary treatment, endocrine ablation was included in the first course of therapy among 233 women and was part or all of the subsequent treatment for 209 patients. However, ablative procedures were performed in the first or subsequent course among only 26 of the women 55 years of age or older and among 61 women classified as remote or unknown stage of disease at diagnosis. Thus, when only the 2,032 women less than 55 years of age with localized and regional stage of disease are considered, there were 178 or 8.8 per cent treated during the first course and 180 or 8.9 per cent subsequently treated by endocrine ablative procedures. This preliminary analysis is restricted to comparisons among these 2,032 cases.

Table II presents the observed survival from the date of diagnosis as computed by means of the actuarial method[1] for this selected group of women according to the type of therapy supplemental to mastectomy that they received during first and subsequent courses. The five-year survival rate of 51.4 per cent for those 178 patients treated by endocrine ablation during the first course compares favorably with the rate of 49.6 per cent for those 428 patients known to have received other therapy (primarily radiation).

Likewise, when survival is measured from the date of diagnosis, those 180 patients receiving endocrine ablative procedures subsequent to the first course of therapy had a five-year observed survival rate of 25.8 per cent compared to 20.9 per cent for those 248 patients receiving other treatment.

It should be noted that the reporting to the registry of therapy the patient receives after her first hospital admission is undoubtedly incomplete, especially for those procedures that can be performed on an outpatient basis or in the physician's office. This is one of the reasons the present analysis is only preliminary in nature. An extensive effort is now being made to obtain as complete information as possible on the total treatment picture for each cancer patient especially as to additional therapy outside of the hospital which most frequently is either radiation and/or chemotherapeutic and hormonal drugs.

If all endocrine ablation in the first and subsequent course of therapy is arbitrarily considered to be prophylactic and therapeutic castration, respectively, then it is possible to consider changes over time in the use of castration following radical mastectomy for breast cancer in Connecticut. Ryan, et al[2] studied the experience with prophylactic and therapeutic castration in seven of the largest Connecticut hospitals during the years 1949 through 1953 and their results, along with comparable cases from the present study, are shown in Table III.

TABLE II

Survival rates by initial and subsequent therapy: Female breast cancer cases, localized and regional stage, less than 55 years of age, with radical or simple mastectomy as primary treatment, Connecticut, 1957-62.

COURSE AND TYPE OF THERAPY	NO.	SURVIVAL RATE (%) 1-YR.	3-YR.	5-YR.
Total cases[1]	2032	95.7	77.0	64.3
Initial therapy included:				
Endocrine ablation	178	90.3	60.9	51.4
Other therapy	428	91.5	63.7	49.6
No additional therapy	1426	97.7	83.1	70.3
Subsequent therapy included:				
Endocrine ablation	180	95.5	54.9	25.8
Other therapy	248	92.7	45.0	20.9
No additional therapy	1604	96.2	85.7	79.3

[1] Only 6 of these 2032 cases were not known to be histologically confirmed.

TABLE III

Distribution of cases by castration status and time period of diagnosis: Female breast cancer cases, localized and regional stage, less than 55 years of age, with radical mastectomy as primary treatment.

CASTRATION STATUS	7 CONNECTICUT HOSPITALS, 1949-53[1] NO.	%	38 CONNECTICUT HOSPITALS, 1957-62 NO.	%
Total cases	656	100.0	1916	100.0
Prophylactic castration	80	12.2	164	8.6
Surgery	38		156	
Radiation	42		8	
Therapeutic castration	70	10.7	172	9.0
Surgery	47		171	
Radiation	23		1	

[1] From Ryan, et al (2).

There appears to be a slightly lower percentage of castrated patients in the more recent time period. This is not due to the fact that the experience of the smaller hospitals in the state has been included in the present analysis. It is readily apparent that castration by means of irradiation, a popular technique around 1950, was very seldom performed in the state a decade later.

TABLE IV

Survival rates by castration status and time period of diagnosis: Female breast cancer cases, localized and regional stage, less than 55 years of age, with radical mastectomy as primary treatment.

	TIME PERIOD OF DIAGNOSIS	
CASTRATION STATUS	7 CONNECTICUT HOSPITALS, 1949-53[1]	38 CONNECTICUT HOSPITALS, 1957-62
Total cases	644	1916
Survival rate (%)		
1-year	94.4	96.0
3-year	75.5	77.6
5-year	65.2	64.9
Prophylactic castration	72	164
Survival rate (%)		
1-year	92.0	90.8
3-year	81.1	62.4
5-year	72.5	51.8
Therapeutic castration	67	172
Survival rate (%)		
1-year	95.8	95.3
3-year	73.8	54.6
5-year	53.4	25.9

[1] From Ryan, et al (2). Survival rates were adjusted for normal mortality and are therefore 2 or 3 per cent higher than observed rates. Twelve patients pregnant at diagnosis were not included in the survival analysis.

A comparison of survival rates following radical mastectomy and either prophylactic or therapeutic castration is shown for the two time periods in Table IV. The survival experience for all patients, castrated and not castrated, in the two time periods is almost identical. However, patients diagnosed during the years around 1960 and having castration as part of their therapy have substantially lower long-term survival rates than do comparably treated patients diagnosed around 1950. An explanation of this interesting observation is not readily available.

Total survival time from diagnosis to death is undoubtedly the most important interval to consider in any study of the quantity of survival.[3] This interval has been utilized in all analyses of the Connecticut Tumor Registry data so far presented. In order to investigate other intervals of interest that have not been routinely coded for the registry data, e.g., from recurrence to death, the case records of 192 patients included in the registry and

TABLE V

Distribution of cases and survival values[1];
Personal series of 192 advanced breast cancer cases.

	TOTAL CASES NO	%	CASTRATED CASES ONLY NO.	%
Total number of patients	192	100.0	70	100.0
Primary treatment:				
Radical mastectomy	161	83.9	60	85.7
Simple mastectomy	14	7.3	6	8.6
No mastectomy	17	8.9	4	5.7
Stage of disease at diagnosis:				
Localized	54	28.1	11	15.7
Regional	110	57.3	47	67.1
Remote	21	10.9	9	12.9
Unknown	7	3.6	3	4.3
Age at diagnosis:				
Less than 55	113	58.9	67	95.7
55 or older	79	41.1	3	4.3
Average	51.6		41.5	
Months from diagnosis to recurrence:				
Mean	35-38		30-34	
Median	21-25		18-22	
Months from recurrence to death:				
Mean	25-26		25-27	
Median	18-20		18-21	
Months from diagnosis to death:				
Mean	60-64		56-61	
Median	47-50		48-52	

[1] Two values are shown for each mean and median: (value based on dead cases only)—(value based on dead and alive cases)

all of whom were managed by a leading medical oncologist in the state, were reviewed with particular regard to the time of recurrence. An analysis of the entire series (Table V) revealed data on primary treatment, stage of disease, and age at diagnosis which show these cases to be comparable to series reported by other authors.

The 192 patients were all diagnosed between 1940 and 1963 (over 80 per cent since 1955). All were followed until death except for 31 patients still alive at the time of the analysis. Follow-up information was available into calendar year 1965 on all but 3 of the 31 patients still alive.

Survival values are shown in Table 5 for all 192 cases and separately for the 70 patients castrated either prophylactively (19 cases) or therapeutically (51 cases). There is little difference between the survival experience of the castrated patients and the total series. The mean and median survival values for the castrated patients can reasonably be compared to other reports in the literature (e.g., 3, 4) and it can be stated that the survival in this small Connecticut series appears to be quite favorable.

There were 162 patients in this series who received a combination of chemotherapy plus medical hormones as secondary treatment for their advanced disease. Hormones alone were included in the treatment of 53 patients. Adrenalectomy was performed on only 16 patients and hypophysectomy on but 6 patients. The survival experienced by this series suggests that a planned, deliberate and sophisticated program emphasizing medical, hormonal and chemotherapeutic treatment may yield results as favorable as under a program stressing major endocrine ablative procedures.

Discussion And Conclusions

The purpose of this investigation was to examine the data collected in the Connecticut Tumor Registry on the type of treatment regimes in the management of advanced breast cancer and to evaluate the results obtained by such therapeutic approaches. Although the results presented here are only tentative, observations on the use and the results of castration in the time period 1957 to 1962 as compared with about a decade earlier are of interest. Castration by radiation is rarely done anymore and the percentage of those females being surgically castrated either early or late has not changed appreciably between 1950 and 1960. The 5-year survival rate of all castrated patients appears to have decreased, especially so in the therapeutic group.

Results following prophylactic castration were superior to those obtained for patients therapeutically castrated based on the 3 or 5-year survival rates. Rough estimates of median survival obtained from the data shown in Table IV for Connecticut residents are at variance with the findings reported by Kennedy, et al[3] for residents of the upper midwestern United States. In the "homogeneous castration series" of those authors, there were 108 prophylactic castrations and 105 therapeutic castrations (or as Kennedy suggested they be termed "early" and "late" castration) with median intervals of survival from initial therapy to death of about 3 years for both castration groups. Median survival from diagnosis to death computed from the data for either time period shown in Table 4 is slightly greater than 3 years for the therapeutic castration group but in excess of 5 years for the prophylactic castration group.

The data on 192 advanced breast cancer cases treated by one medical oncologist were studied in depth. It can be stated that the survival in this small Connecticut series appears to be as favorable or more so than that presented by several other investigators. The survival experienced by this Connecticut series, primarily receiving hormones combined with chemotherapeutic drugs as secondary therapy for their widespread metastases, suggests that a conservative program emphasizing medical hormones and chemotherapy may yield results as favorable as a program of major endocrine surgery which has such a position of prominence today. Further evidence in this direction could possibly lead to the conclusion that hormonal and chemotherapeutic drugs in the treatment philosophy of advanced breast cancer could eventually replace major endocrine extirpation therapy as was hinted at by Landau.[5]

The results described so far become even more important when one considers not only the quantity but the quality of survival. While these present investigations were primarily concerned with the number of patients surviving, it is always important to reflect on the way they survive while considering the choice of treatment modalities. It has been so very aptly stated by Hayward[6] that "in the treatment of advanced breast cancer the survival rate is probably less important than the quality of survival." In all approaches to treatment regimes, but especially in those affecting the advanced breast cancer patients, "if major operative treatment is considered, then the benefit to be accrued must be worth while." We concur with this philosophy.

Acknowledgements

We wish to thank Dr. Henry Williams, Medical Oncologist, Hartford Hospital, and Assistant Professor of Medicine, Yale School of Medicine, for his permission to review his patients' records and for the money he made available to us through the Cancer Control Fund, Hartford, Connecticut, to accomplish this. We also wish to extend thanks to those in the Tumor Registry who have helped to produce the basis for the statistics for this investigation.

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THE PRESIDENT'S PAGE

New Dimensions For Health Care

One result of the *simultaneous* progress in science and changes in our national socio-economic structure is the current widespread interest in efforts to eradicate the root-causes of ill health. Improved communication and easier travel have led to a better understanding of the need for these efforts. Government now considers health care a major issue. Consequently, while the search for the basic etiology of categorized disease entities continues with unprecedented vigor, numerous other programs have been initiated which are beamed at the elimination, or at least diminution, of factors having less direct, but important, causal-relationship to illness.

Physicians have long been aware that many environmental factors enhance the probability and sustain a high incidence of disability. An enlightened Public, more than ever conscious of the burdens of illness which increasingly affect the welfare of our entire society, is now seeking methods of corrective action. To be sure this interest may be partly related to the fear of disturbed national economy, decreased productivity and other like risks. The sincere concern with water and air-pollution and with accidents on our highways is clear evidence of aroused communities. They recognize that the solution of these problems involves cooperation of many factions having overlapping, and often vested, interests. In this respect the medical Profession may be expected to assume more than a traditional role in community efforts to protect its citizens from hazards to health.

A superficial look at the high prevalence of alcoholism, extensive narcotic addiction, and widespread use of tranquillizers is sufficient to indicate the need for critical analysis of a cause-and-effect relationship to the stresses associated with the "way-of-life" of our society. It is urgent and perhaps more practical that the Profession energetically assist in community educational, or other, movements designed to alleviate presumptive causes while awaiting more definitive answers to these medical-social problems. Objectives such as preservation of recreational areas accessible for use by the people, assistance to underprivileged neighborhoods or "ghettos," promotion of facilities for cultural enrichments of the "masses," and intelligent family-planning are integral parts of any plan for the improvement of total (physical and mental) health and "human betterment."

As a result of the recent adoption of new methods of financing such as medicare and a rapidly developing attitude that good health is the "right" of the citizen, there is increasing emphasis on the demand for the provision of *total* health care. Of necessity doctors have largely concentrated on the *treatment* of disease. Although some active and passive methods of *prevention* of disease have long been employed by the Profession, it is probable that new demands by the Public for the preservation of good health will lead to further development and more extensive use of medical and social techniques of preventive care in the future. If hope can be converted into achievement, the reduction in human suffering and costs of illness can be gigantic.

Orvan W. Hess, M.D.

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CALL

ANNUAL MEETING OF THE HOUSE OF DELEGATES

The 1967 Annual Meeting of the House of Delegates will be held at the Hartford-Hilton Hotel, Hartford, commencing at 9:00 o'clock in the morning of Tuesday, April 25.

Following luncheon, the House will reconvene for the completion of business.

Orvan W. Hess, President
Kenneth F. Brandon, Speaker of the House
Waldo E. Martin, Secretary

INTRODUCTION OF RESOLUTIONS

Article V, Section 12, Par. 3 of the Bylaws of the Society Provides that:

All resolutions to be considered as regular business at any regular meeting of the House of Delegates must be in the hands of the Speaker not later than seventy-two hours before the opening of that meeting. All resolutions and recommendations published in the official agenda distributed to the members of the House prior to the meeting at which action is to be taken shall be considered as regular business. Resolutions presented later than seventy-two hours before the opening of a meeting will be referred for consideration as regular business by the House only when they are presented by the Council or accepted for consideration by majority vote of the delegates present. Any resolution which does not qualify in accordance with the aforesaid provisions for consideration as regular business may be accepted for action by a majority vote of the delegates present and, if so accepted, shall be referred at once by the Speaker to a reference committee. Any such reference committee shall consider resolutions referred to it and shall report, with recommendations to the House before adjournment of the meeting.

PROPOSED AMENDMENT TO THE BYLAWS

The following proposed amendment to the Bylaws was presented to the House of Delegates on December 8, 1966 and were tabled for consideration and action at the next regular meeting of the House of Delegates.

In accordance with the Bylaws, this amendment will be published in Connecticut Medicine, "on one or more occasions prior to the next meeting . . . at which meeting the amendment shall be taken off the table and acted upon by the House of Delegates."

INTRODUCED BY THE COUNCIL:

The Committee(s) On Public Relations

Objective: To abolish the present two-committee PR Divisional structure (totalling 19 members) and to provide for the annual election of a single large committee of 24 members. By so doing, it is hoped to increase the effectiveness of the PR Division by having more participants numerically; to assure having adequate county-by-county representation at all meetings of the Division; and to stimulate greater interest in public relations activities at state and county levels through a continuing two-way exchange of ideas.

Proposed Amendment: Article XI—DIVISIONAL BOARDS AND COMMITTEES.

(I) Section 3.—Divisional Standing Committees

Par. (E)—Public Relations Division

Delete: Committee on County and Local Public Relations. Committee on State and National Public Relations

Substitute: Committee on Public Relations

(II) Section 5.—Duties of Standing Committees

Delete: Present Paras. 16 and 17 (describing present 2 committees)

Substitute: New Par 16 as follows:

Par. 16 COMMITTEE ON PUBLIC RELATIONS. The Council shall annually nominate to the House of Delegates a Committee on Public Relations of twenty-four members of The Society and shall nominate the chairman thereof. The nominations shall be made as follows: Eight members recommended for nomination by the component county medical associations, on the basis of one per county; eight additional members selected by the Council, on the basis of one from each county; and the other eight members to be selected at-large. The function of the Committee shall be to inquire into and pass upon such phases of public information as deal with the care of the sick and the practice of medicine, to keep the people of Connecticut accurately and reliably informed concerning matters of public interest in the field of medicine, to encourage cordial relations and understanding with communications media and to cooperate with other committees of the Society and of the AMA in a program of public relations. The Committee shall assist the committee on public relations of the component associations in developing and disseminating accurate and reliable information concerning matters of public interest in the field of medicine and shall use its efforts to encourage cooperation by the committees on public relations of the component associations with local medical societies, allied professional groups, voluntary agencies, the press, radio, television and other groups within the respective counties in a program of public relations.

(III) Renumber present Paras. 18 through 29 to become Paras. 17 through 28.

Delegates To Annual Meeting

The Bylaws of the Society provide that each county association is entitled to one delegate in the House of Delegates for each thirty-five Active or Life Members in the association or fraction thereof based on the membership as of December 31st of the immediately preceding year. According to this, the quota of delegates from each county association who should attend the Annual Meeting of the House of Delegates which will be held in Hartford, April 25, 1967, and the Semi-Annual Meeting in December, 1967, is as follows:

County	*Membership Dec. 31, 1966*	*Official Delegates*	*County*	*Membership Dec. 31, 1966*	*Official Delegates*
Fairfield	953	28	New Haven	1019	30
Hartford	1120	32	New London	206	6
Litchfield	150	5	Tolland	29	1
Middlesex	121	4	Windham	74	3

Election Of Councilors And Associate Councilors

Councilors and Associate Councilors, who shall serve for two years, shall be elected this year at the annual meeting of each of the county association in Hartford, Middlesex, New London and Windham counties. In accordance with the Bylaws, each component association having over 750 members may elect one additional Associate Councilor. Therefore, the Hartford County Medical Association shall elect a Councilor and two Associate Councilors for a two year term.

No Councilor or Associate Councilor elected by a component association shall serve more than three successive terms of two years each in his respective office, but after a lapse of one term of two years, such Councilor or Associate Councilor shall be eligible for reelection.

Newly elected Councilors and Associate Councilors shall not assume office until after the Annual Meeting of the House of Delegates.

An Acknowledgement

Recently it was brought to the attention of the president of the Society that this year's Annual Meeting and Scientific Assembly on April 25-27 will partially conflict with the Passover Holidays. In a letter to a member who wrote to him concerning this matter, President Orvan W. Hess replied: "Please be assured that you have the expressed regrets of the Council, as well as my own, that this conflict will occur." . . . "As you may know, our annual meetings have to be planned nearly a year in advance . . . (and) . . . in this instance, apparently, there was a 'blind spot' last summer (when the Council selected the dates) with respect to the Passover observances in 1967." . . . "You are correct that it would be impossible to reschedule the various programs at this late date, but please understand that the oversight was entirely unintentional and that we will make special efforts in the future to eliminate the possibility of this or similar conflicts coming about."

SUMMARY OF ACTIONS

COUNCIL MEETING

Wednesday, January 11, 1967

I. Attendance

Present in addition to the Acting Chairman, Dr. Orvan W. Hess, were: Drs. Bradley, Gardner, W. Martin, Brandon, H. Caplan, Polivy, Rogol, Grendon, Abbot, Spitz, Hastings, Shepard, Ayres, Cramer, Fabro, Grant, Petrie, Pelz and Wilson. Also present were: Mrs. Lindquist, Mr. Villano, Mr. Chilcoat (AMA), Dr. John Donnelly (CSMS Committee on Mental Health) and Dr. Richards.

Absent were: Drs. Goldberg, M. Caplan, S. J. Martin, Egan, Nolan, Ciccarelli, Palomba and Roch.

II. Routine Business

Approval Of Minutes

As printed and distributed, it was VOTED to approve the minutes of the meeting of December 21, 1966.

Election Of Student Member

It was VOTED to elect to Student Membership one Connecticut resident who is attending medical school as follows:

John E. Sawicki
Meriden, Connecticut
George Washington School of Medicine—Class of 1969
Parent—Edward J. Sawicki

Representative—AMA Conference On Emergency Medical Service

It was VOTED to direct the Chairman and the General Manager to appoint a member of the Society to attend this Conference as a CSMS representative and to report to the Council on the proceedings thereat. After considering several names suggested by members of the Council, this appointment was made as follows:

J. Benton Egee, Newtown

Gift To Connecticut Physicians' Art Association

It was VOTED to sponsor an art exhibit at the Annual Meeting in April, to be arranged and conducted by the CPAA, and to cover expenses attendant thereto in an amount up to $200 out of General Funds.

Date Of Next Meeting

The next meeting of the Council will be held on Thursday, February 16, 1967.

III. Old, New And Special Business

Report—Ad Hoc Committee On Physician-Hospital Financial Arrangements

It was VOTED to accept a report filed by this Ad Hoc Committee, concerning "open" policy for hospital medical staff appointments, and to place the report on the agenda for discussion at the next Conference of County Medical Association Officers. Subsequent to discussion of the report at that Conference, copies are to be sent to the governing boards of all component county medical associations and possibly to other interested parties. It was VOTED to table several motions calling for distribution of the report to outside agencies at this time.

The "Millis Report" On Graduate Education Of Physicians

Pursuant to a recommendation made by Michael A. Dean, Bridgeport, Acting Delegate to the AMA at the recent Las Vegas meeting, it was VOTED to refer the AMA's "Millis Report" to the CSMS Committee on Postgraduate Education for study and report (with recommendations) to the Council. Since the Millis Report will come before the AMA House of Delegates in June for definitive action, it was Dr. Dean's feeling that the Society's Delegates should be advised of state-level reaction to the Report and its implications.

Representative—Advisory Committee On Title XIX MA Program

At the request of Welfare Commissioner, Bernard Shapiro, it was VOTED to recommend Orvan W. Hess, New Haven, as a CSMS representative on the Advisory Committee to the State Welfare Commissioner on Medical Care Services, as required by Title XIX of P.L. 89-97.

Legislation—1967 General Assembly

The Council reviewed a number of matters concerning legislation which will come before the General Assembly at the 1967 session, and took actions thereon as follows:

(1) With minor editorial changes, it was VOTED to approve the draft of a Society-sponsored bill titled: An Act concerning Payments for Services of Physicians Under Medical Assistance Programs Implementing Title XIX of P.L. 89-97. In brief, the bill calls for the State to pay physicians their "usual and customary charges" for services rendered to Title XIX beneficiaries; defines the meaning of "usual and customary charges"; and provides that, on questioned claims for payment, the Welfare Commissioner or his agent shall seek the opinion of an appropriate County Medical Association.

(2) With minor editorial changes, it was VOTED to approve the draft of a Society-sponsored bill titled: An Act concerning Interference with the Rights of Beneficiaries Receiving Medical Assistance under Title XIX of P.L. 89-97. In brief, the bill prohibits any individual or agency, public or private, from acting to deny MA beneficiaries of any of their rights, or to interfere with or control the practice of medicine by licensed physicians or the manner in which medical services are customarily provided.

(3) Having heard John Donnelly, Chairman of the CSMS Committee on Mental Health, outline the provisions and purposes of a comprehensive "package" of legislation which will be introduced on drugs and drug addiction, it was VOTED to give the Society's support to the legislative program on drug control and the treatment of drug addiction recommended by the Committee on Mental Health. Several details of the proposed legislation (such as a requirement that prescriptions be written in triplicate) will be opposed.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on January 11, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

Around The State

New Haven County

The Business meeting of the 183rd Annual Meeting of the New Haven County Medical Association will be followed by the 14th Annual Joint Dinner with the Woman's Auxiliary to the New Haven County Medical Association.

This will be followed by the Presentation of the Plaque to the Past President.

The after dinner program will include: performance by Miss Pattie Bayne, magician-comedian followed by entertainment by Mr. Al Flosso, known as the "Coney Island Fakir," popular comedian.

Date—Thursday, March 30, 1967
Place—Waverly Inn, Cheshire
Time—Business Meeting—3:30 p.m.
Dinner—7:00 p.m.

Board Of Governors

New Haven County Medical Association

January 26, 1967

The Board of Governors of the New Haven County Medical Association met at the Graduates Club on Elm Street, New Haven, on Thursday, January 26, 1967 at 4:30 p.m., with Max Caplan presiding.

Reports on the latest Medicare and Medicaid problems which came before the Council were reported by our Councilors Frank Abbot and Stewart Petrie.

A letter was read to the Board which brought to its attention the Department of Public Health of the Yale Medical School has received a Federal grant of nearly $260,000. for a "Study of total medical Care." Part of this study, it is reported, will be the possibility of a "closed panel" medical care program for the members of a large labor union and their dependents and a similar program for the Yale University Family.

It was voted unanimously that the Clerk be directed to send letters to Senators Ribicoff and Dodd and all of Connecticut's members of the House of Representatives calling their attention to this grant of taxpayers' moneys. The Board, as physicians and taxpayers, objected to this on two counts: (1) it is reduplicative with respect to other grants which have already been made for the same purpose; and (2) it is morally wrong to use public moneys for any type of study that is almost certain to find that private medicine, as a free enterprise calling, ought to be done away with and replaced by a tax-supported centralized system.

The close of the business meeting was followed by a social hour and dinner.

Respectfully submitted,
H. A. Levin, M.D., Clerk

A.M.A.—116th Annual Convention

Atlantic City, New Jersey

June 18-22, 1967

The 116th Annual Convention of the American Medical Association will be held in Atlantic City June 18-22 this year. Convention Hall and surrounding hotels will house the Scientific Program; the House of Delegates will meet at the Chalfonte-Haddon Hall Hotel.

Among special presentations planned are four general scientific sessions on backache, healing, patient care, and sex.

The 22 Scientific Sections will offer programs individually, and many will hold joint meetings on subjects of common interest. A full schedule of medical motion pictures is planned. At least five color telecasts will be broadcast, live from a Philadelphia hospital in cooperation with the University of Pennsylvania School of Medicine.

The General Scientific Meetings are open to all physicians attending the Annual Convention.

Other General Scientific Meetings on this year's Annual Convention program will be on the subject of: backache, healing and sex.

In addition to the General Sessions, each of the 22 Scientific Sections will present scientific programs. Many of the Section programs will, as in past years, be joint meetings of two or more Sections and, in some instances, a specialty society.

Specialty societies joining AMA Sections will include:

—The American College of Chest Physicians, which will join the Section on Diseases of the Chest for a program.

—The American College of Cardiology, which will join the Section on Internal Medicine in a session.

—The Society for Investigative Dermatology, Inc., which will hold its meetings in conjunction with the Section on Dermatology.

New From Yale University School Of Medicine

The key component of the system, to record fetal electrocardiography developed by Dr. Edward H. Hon, Associate Professor of Obstetrics and Gynecology at the Yale School of Medicine, is a new kind of electrode that attaches to the scalp of the unborn child while it is in the mother's uterus. The device provides the most clearly defined fetal electrocardiogram (ECG) patterns that have ever been recorded.

Fetal electrocardiograms are studied for alterations in waveform that may indicate problems in the unborn baby. In addition, the timing of the successive fetal ECG's is used to monitor the fetal heart rate continuously during labor and delivery. Clinically, deviations from the normal range of 120 to 160 beats per minute are considered signs of distress in the fetus. Unless they can be corrected promptly, immediate surgical delivery of the baby is necessary to prevent its death or irreversible damage to its health.

Dr. Hon has been doing research on fetal electrocardiography for the past ten years and has developed a number of techniques for improving the quality of fetal ECG recordings. Obtaining the ECG of an unborn baby is a difficult technical problem because of the inaccessibility of the fetus. Fetal ECG's that are recorded from outside the maternal abdomen are about ten microvolts in amplitude, or only 1/100th the size of the adult ECG. With the new type of electrode—which is attached directly to the fetus—the average fetal ECG is about 300 to 400 microvolts in amplitude, and signals as high as 800 microvolts have been recorded.

Symposium Announcement

The Kidney Foundation of Connecticut, an affiliate of the National Kidney Foundation, announces the Third Symposium on Kidney Disease to be held at the Hotel America, Hartford, Connecticut on Thursday, April 13, 1967.

Program sessions 9:00 A.M. to 5:00 P.M. Registration Fee $10.00 (this includes luncheon). Courtesy registrations (do not include luncheon) are available for house staff, research fellows and nurses upon request from their supervisor.

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BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

A Primer of Electrocardiography. Fifth edition, George E. Burch, M.D., F.A.C.P., F.A.C.C. and Travis Winsor, M.D., F.A.C.P. Lea & Febiger, Philadelphia, 1966. 304 pp., 286 illustrations. $6.50.

Effective Writing For Engineers-Managers-Scientists. H. J. Tichy, John Wiley & Sons, Inc., New York, London and Sydney, 1966. 337 pp. $5.95.

Nobel Symposium I. Muscular Afferents And Motor Control. Ragnar Granit, John Wiley & Sons, New York, London and Sydney, 1966. 466 pp., $20.00.

Radiology in World War II. Prepared and published under the direction of Lieutenant General Leonard D. Heaton, The Surgeon General, United States Army. Editor in Chief, Colonel Arnold Lorentz Ahnfeldt, MC, USA, Editor for Radiology, Kenneth D. A. Allen, M.D., Assoc. Editor, Elizabeth M. McFetridge, M.A. and Assoc. Editor, Mindell W. Stein, B.Sc. Office of the Surgeon General Department of the Army, Washington, D. C. 1966. 1132 pp. with 317 illustrations, 8 charts, 14 maps and a comprehensive index. $8.25.

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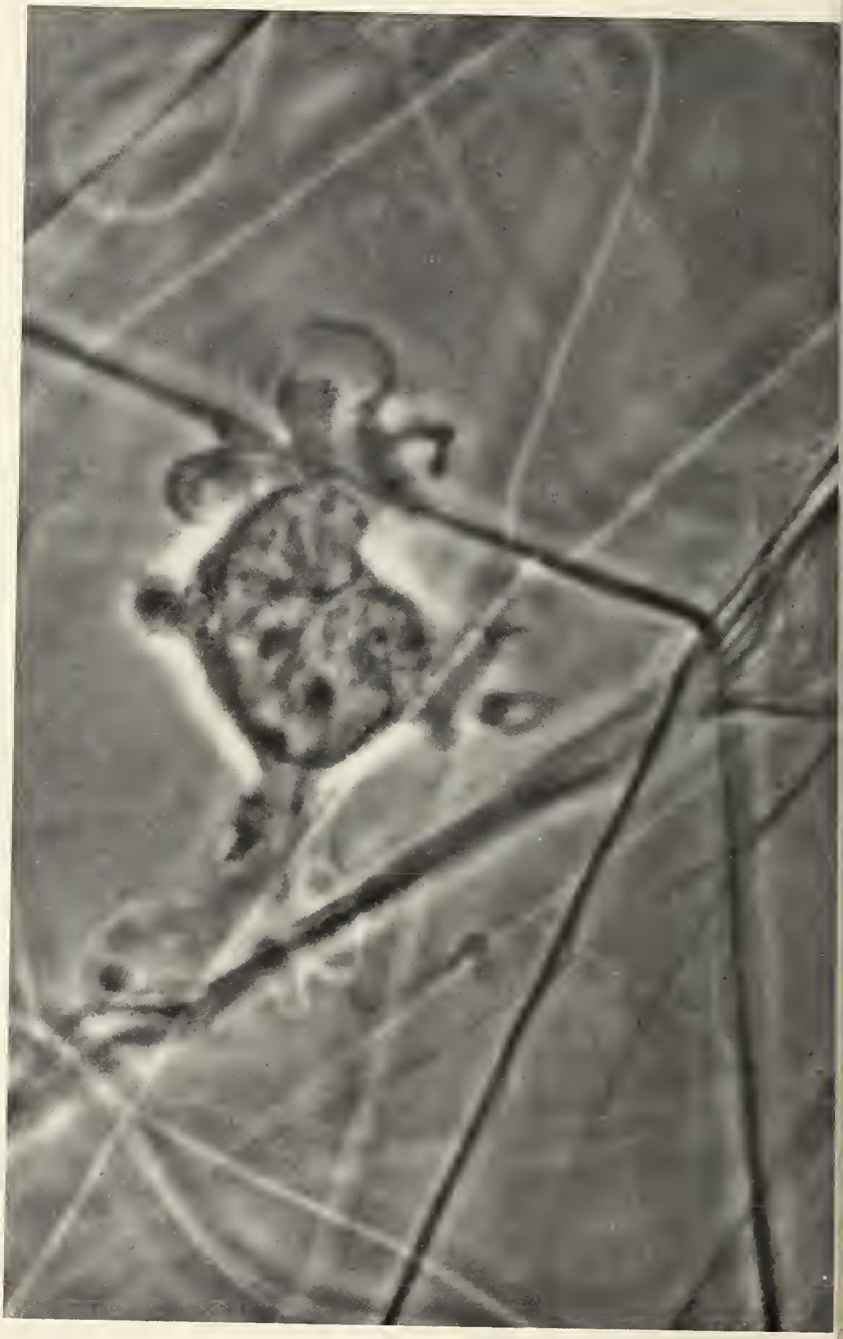
INFLAMMATION:

A cellular fight for life

A SYNTEX REPORT based on recently developed hypotheses about topical corticosteroids, including the cellular theories of inflammation by Thomas F. Dougherty, Ph.D., University of Utah.

You are looking at a fibroblast fighting for life. This cell—one of the most common found in connective tissue—has literally been poisoned by cytotoxins released from other cells that have ruptured. Soon, if the abnormal activity of this fibroblast does not cease, it, too, will rupture and die—one more casualty in the inflammatory wave of destruction precipitated by injury.

Until a short time ago no one had ever witnessed such a scene at the cellular level. Now, through advanced cinemicrographic techniques, it is possible to view and photograph the inflammatory process as produced experimentally in living animal tissue. This method permits new insight into the mechanism of inflammation and the role of corticosteroids in therapeutic management. Equally important, these techniques shed new light on factors that may make one corticosteroid more effective than another—factors that can be correlated with other chemical, biologic, and clinical parameters.



PLACEMENT OPPORTUNITIES

PEDIATRICIAN—Large multi-specialty group is looking for fourth man for Department of Pediatrics in a large city in northern Connecticut.

WANTED: G.P. or Internist for General Medical and Surgical accredited State Veterans' Hospital. Duties are those of ward officer on general medical ward. Older physicians; retired or semi-retired; full-time or part-time; up to age 65, if still vigorous, are acceptable. Many fringe benefits. Apply: Personnel Officer, State Veterans Home and Hospital, Rocky Hill, Connecticut.

RADIOLOGIST — 350-bed general hospital needs third radiologist for general diagnostic work. Isotopes, therapy and special procedures available, if interested. A new 9-room department is being built. Salary $25,000 with yearly increments. Contact: Howard F. Root, M.D., c/o Department of Radiology, New Britain General Hospital, New Britain, Connecticut 06050.

HOUSE PHYSICIAN—Diversified duties in 135-bed accredited voluntary hospital. Connecticut license required. Monday through Friday and every other Saturday morning. Salary: $15,000 yearly plus 3-room furnished apartment. Contact: Administrator, Park City Hospital, Bridgeport, Connecticut 06604. Telephone: Area Code 203, 368-0201,

OBS-GYN—Board certified Obs-Gyn needed to associate with another Obs-Gyn in large, industrial city in Southern Connecticut, leading to eventual partnership.

HEALTH DIRECTOR—City of Stamford, population 100,000 needs physician with a degree in Public Health, with administrative experience, and willing to assume leadership in expanding and coordinating the health activities of the community can command a salary equal to or higher than any in the area. Contact: Frank H. D'Andrea, M.D.; Chairman, Health Commission; 750 Summer Street; Stamford, Connecticut 06902.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

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G.P.—30 years of age, military obligations completed. Wishes to practice with either a group or an associate in the Guilford area.

INTERNIST—33 years of age, Board eligible, military obligations satisfied. Wishes to practice with a group in a medium to small community.

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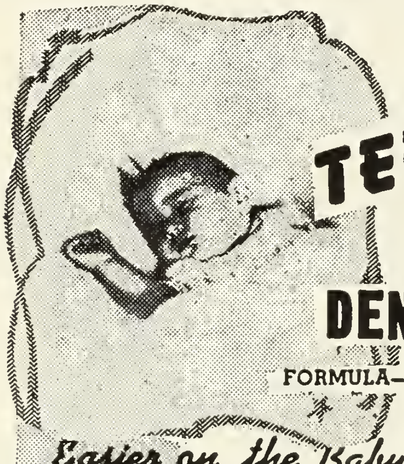

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DENTOCAIN LOTION MILD makes it easier to go through the troublesome teething period. A small amount, applied with gentle massage, brings quick, soothing relief to irritated and inflamed gum tissue, aids in getting infant back to sleep.

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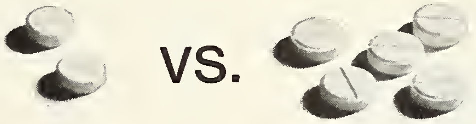
For effectiveness, economy, and convenience, therefore, Hygroton is the diuretic to choose to start with and the one to stay with.

*Brest, A. N., et al.: J. New Drugs 5:329, 1965.



Natruresis above control values after maximum recommended doses (mEq./24 hours) in "normal" patients

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Warning: With administration of enteric-coated potassium supplements, the possibility of small bowel lesions should be kept in mind.
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OBITUARIES

Ralph Moore Tovell, M.D.
1901 - 1967

Dr. Ralph Moore Tovell died at Hartford Hospital on January 7, 1967, after a long illness. With his passing, one of the great pioneers of anesthesiology was laid to rest; and laid to rest, surely, with the certain satisfaction of knowing that the efforts of an entire professional lifetime had contributed pricelessly toward the development of a burgeoning young specialty into an established medical discipline.

Ralph Tovell was born in Sydenham, Ontario, in 1901, the son of a physician. He was educated at Queens University in Kingston, Ontario, where he received his A.B. and M.D. degrees. He served an internship at the Kingston General Hospital, and went on to further training in obstetrics at the Lying-In Hospital, New York City. Then, in 1929, he entered the virtually unknown specialty of anesthesia as one of the first residents in this country, accepting a post as Fellow in the Section of Anesthesia at the Mayo Foundation. He received the degree of M.S. (Anesthesia) from the Graduate School of the University of Minnesota, and remained at the Mayo Clinic as an Associate in the Section of Anesthesia under his teacher and lifelong friend, Dr. John Lundy, until 1936, when he was called to Hartford Hospital to be Director of, and develop, the Department of Anesthesia. How well he succeeded is attested to by the fact that his Department became internationally famous and has trained well over two hundred anesthesiologists.

Progress depends, among other things, upon the chance that the right man is available at the right time and in the right place to accomplish what it is necessary to accomplish. Ralph Tovell was such a man. He helped to nourish and mature the American Society of Anesthesiologists, and became its President in 1941. He was a founder, for many years a Director, and later President, of the American Board of Anesthesiology. He was chiefly responsible for the creation of a Section of Anesthetists in the Connecticut State Medical Society; and then for transforming it into today's Connecticut State Society of Anesthesiologists. He was one of the founders, for many years an Associate Editor, and then Editor, of *Anesthesiology,* the national journal of the specialty in this country. He was a leading light in the Academy of Anesthesiology, and served as its President in 1955. He was one of the indefatigable workers who helped to create the Section of Anesthesiology of the American Medical Association, and was Chairman of the Section in 1948.

He became a naturalized citizen of the United States in December of 1940, and in 1942, he entered the United States Army and served as Senior Consultant in Anesthesiology in the European Theater throughout World War II, being discharged with the rank of Colonel in 1945. His proven abilities during military service led to his appointment after the War as Consultant in Anesthesiology for the Veterans Administration Central Office; as Chairman of its Board of Chief Consultants; and as Consultant in Anesthesiology to the Office of the Secretary of Defense.

His work during the War, and his services to his specialty throughout his career, earned him many justified honors, including the Bronze Star, the Medaille de la Reconnaissance Francaise, the Legion of Merit, Frederic Hewitt Lecturer at the Royal College of Surgeons in London, Honorary Fellow of the Royal Society of Medicine (London), and Distinguished Service Award of the American Society of Anesthesiologists, Honorary Fellow of the Association of Anaesthetists of Great Britain and Ireland, Fellow of the Faculty of Anaesthesia of the Royal College of Surgeons, and the Merit Award of the Horace Wells Club of Connecticut.

For those of us who had the privilege of studying under and working with Ralph, the most vivid memories will be the boundless energy of his mind, the cheerfulness and humor of his friendships, and his unostentatious love of his family.

He had the imagination to envision, the daring to act, and the ability to accomplish. And what a very great deal he did accomplish! He leaves as a heritage—among many other things—a Department of 26 trained anesthesiologists, some 150 medical writings, and a totally-equipped medical specialty which he was instrumental in founding and developing.

He leaves a legion of friends, here and abroad. They came to Hartford from South Africa and Rochester, Minnesota, and Australia and Wheeling, West Virginia, and Sweden and Kingston, Ontario, and Washington,D.C., and they were always introduced with the approbation, "This is my friend." And they were. They were all his friends. They will miss him sorely.

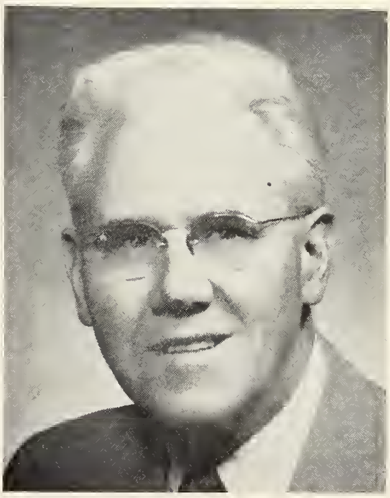
And he also leaves the family from which he derived such pleasure and of which he was so quietly proud: his wife, Bally; his son, Arnold; and his daughter, Mary. To them, the Connecticut State Medical Society extends its deepest sympathies.

David M. Little, Jr., m.d.

Robert Murdoch Miller, M.D.

1898 - 1966

Dr. Robert Murdoch Miller died in the New Milford Hospital on December 28, 1966, of coronary thrombosis, at the age of 68. Dr. Miller was active in the practice of general surgery in New Milford for the past 16 years.



Born in Plainfield, New Jersey, he was graduated from Princeton University in 1921. After a year in which he taught school, he entered Columbia College of Physicians and Surgeons, receiving his M. D. in 1926. He interned at Presbyterian Hospital in New York, and was resident surgeon at The Woman's Hospital, New York City.

Dr. Miller was attending surgeon at Overlook Hospital, Summit, New Jersey, form 1929 to 1951. For a time he was instructor in anatomy at Physicians and Surgeons. For much of his time in Summit he was chief of surgery, and was consulting orthopedic surgeon.

In 1944-5 Dr. Miller interrupted his Summit practice when he and his family went to Labrador, Newfoundland, to serve the International Grenfell Association. He was in charge of its main hospital at St. Anthony during the absence of the director of the medical mission who succeeded Dr. Grenfell.

In New Milford, Dr. Miller has served as chief of surgery and as president of the medical staff of the New Milford Hospital. He was president of the Litchfield County Medical Association in 1962.

He was county chairman of the Committee for Medicine and Religion, and in the summer of 1966 was made state chairman. Dr. Miller was an active member and Deacon of the United Church of Christ, Congregational, in New Milford, where he served on the Religious Education and Social Action Committees. He was also a teacher and superintendent of the church school. He was a strong exponent of integration and equal opportunities. He was a member of the Human Relations Committee of the Greater New Milford Area and of the N.A.A.C.P.

Dr. Miller was a Fellow of the American College of Surgeons, and a member of The Waramaug Medical Society, Litchfield County Medical Association, Connecticut State Medical Society, and the American Medical Association.

Surviving Dr. Miller are his wife, Mary Coates Miller; a sister, Mrs. Harold L. Blood; three sons, Robert, Jr., Arthur, and John; a daughter, Mrs. Richard Kelly; and three grandchildren.

Dr. Miller was a very skillful surgeon. His technique was outstandingly meticulous and painstaking, with caution based on wide experience, but with boldness where it was called for.

He was a searcher for the truth in all things. As a doctor he was always kind and gentle, unsparing of himself, and loved by his patients. He was an inspiration to his colleagues.

Jeffrey Ferris, m.d.

In Memoriam

Kettle, Ronald H.—Deep River; Queens University School of Medicine, 1928. Dr. Kettle was a retired superintendent of Norwich Hospital and had served in this capacity for 30 years. He was a member of the New London County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Kettle died February 2, at the age of 64.

Larkin, Charles L., Sr.—Waterbury, Yale Medical School, 1915. Dr. Larkin was a veteran of the U. S. Army in World War I. He had founded and operated the Larkin Clinic in Waterbury. He was the first president of the Connecticut Cancer Society, and a member of the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Larkin died February 8, at the age of 77.

Lindsay, Marie S.—West Hartford; Tufts College Medical School, 1911. Dr. Lindsay was a member of the Hartford County Medical Association, the Connecticut State Medical Society, the American Medical Association, and the American Psychiatric Association. Dr. Lindsay died December 23, at the age of 77.

Scarbrough, Marvin M. — New Haven; Yale School of Medicine, 1907. Dr. Scarbrough had been a medical examiner for New Haven for 50 years. During World War I, he served as a contact surgeon for the New Haven area. He was a member of the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Scarbrough died January 30, at the age of 88.

Sherman, Hope—Pleasant Valley, Johns Hopkins Medical School, 1925. Dr. Sherman had practiced pediatrics in the Pleasant Valley area for many years. She was a member of the Litchfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Sherman died January 22, at the age of 83.

WOMAN'S AUXILIARY

The Woman's Auxiliary to the Connecticut State Medical Society plans to hold it's Annual Meeting and Tea at our President Rosemary O'Connell's home, 42 Fulton Place, West Hartford, on April 26. This is during the Connecticut State Medical Society's Convention Week. It is usually customary to hold our Annual Meeting at this time so that the women may join their husbands for dinner that evening at the Hartford-Hilton Hotel, Hartford. Annual Reports will be given and the new slate of officers will be voted on.

The Annual Art Exhibit will be held again this year during the Convention week. Any member of a physician's family may enter. Contact Dr. Stewart J. Petrie, President, at 56 Minerva Street, Derby, Connecticut, Mrs. Orvan Hess, Vice President, 29 Old Orchard Road, North Haven, Connecticut, or any of the County Art Chairmen. Hangings will be done at the Hartford-Hilton Hotel on Sunday, April 23. Please get in touch with any of above people if you are not able to bring your art yourself.

The combined A.M.A. and Auxiliary to the A.M.A. Convention has been announced for June 18-22, in Atlantic City, Shelburne Hotel. Make reservations early!—Make a Memo to attend both of these very important and enjoyable events.

IN MEMORIAM

Mrs. E. Roland Hill—Mystic
Past State President

Mrs. Vincent Gorman-Trumbull

CHANGES OF ADDRESS

Notice of change of address should be sent not less than three weeks prior to the date the change becomes effective. Please send the address label from one of the issues you've just received, which shows code numbers to help us make the change promptly, along with the new address and your *zip code.*

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Background Of The Drug Addict

There may not be as much difference as had been thought between the backgrounds of drug addicts and non-addicted delinquents, according to a report in a current American Medical Association publication.

The same conditions of poverty, slums, and broken homes seem to produce both kinds of people, according to a recent issue of the *Archives of General Psychiatry,* published by the AMA.

A 12-year study of 100 New York narcotic addicts shows that there even are surprisingly few differences in the backgrounds of Negro, Puerto Rican, and white addicts. They all had the same problems which seemed to lead to addiction; broken homes, the lack of a "father figure" to give them guidance in early adolescence, and a difference in the two generations' cultural backgrounds.

This latter factor seemed to be the most important in producing an addict, the authors said.

Whether Negro or Puerto Rican, a high percentage of the addicts' families had come from some other culture to New York's urban environment. This difference between the southern U.S. or Caribbean background of the parents and the environment in which the addict grew up seemed to be particularly troublesome as the child neared adulthood.

"At least in part, addiction appears to stem from a lack of adequate identification with the adult role due to events occurring in childhood," the report said.

This 12-year follow-up of 100 New York addicts admitted to the U.S. Public Health Service Hospital, Lexington, Ky., suggests that most addicts "have been deprived, not only . . . by minority group membership and slum residence, but also by physical loss of parents and having been born into a culture different from the one in which their parents lived."

These addicts' delinquency often preceded drug use. Their often inadequate school and job performance occurred despite adequate or superior intelligence.

Although addicts do differ from other delinquents in some ways, the study suggested that urban drug addiction may be best understood by studying general group behavior, not by setting addicts apart as a special social group.

The author is George E. Vaillant, M.D., of the Department of Psychiatry, Tufts Medical School, Boston, Mass.

Patients Don't Always Follow Doctors' Orders

Physicians have long known that some patients don't follow orders for taking medicine, or refuse to take it at all.

A report in the current Journal of the American Medical Association indicates how frequently this can occur. Among a group of Cleveland tuberculosis patients, 15 (30 per cent) of 50 patients were uncooperative about taking one drug, and 14 (42 per cent) of 33 failed to follow doctors' orders for taking another.

"In this era of potent and dangerous medications, patient reliability in taking drugs becomes a primary consideration," the article said. "Most physicians are aware that some patients fail to take prescribed medicines, but few realize the extent of the problem."

The study started with clinic and pharmacy records at the University Hospital of Cleveland, which indicated that 50 persons in the outpatient department were supposed to be taking the drugs isoniazid and/or aminosalicylic acid.

It became apparent large numbers of patients weren't following directions when urine tests failed to reveal any trace of the drugs.

There were 20 men and 30 women patients, ranging in age from 17 to 78, with an average and median age of 45. Forty-eight were known to have tuberculosis. Forty-five were Negro and five, white. All but one lived in a poor downtown section of east Cleveland. Forty-five (90 per cent) understood perfectly the instructions for taking their medicines, the authors said.

"Detection of the patient who is not taking his medicine is difficult," the report said. "Simply asking him seems unsatisfactory since patients tend to claim that they have taken medicine when direct evidence indicates that they have not.

An earlier study, for instance, indicated that 83 per cent of families claimed to have given a full 10-day course of penicillin to their children when evidence indicated that 82 per cent had stopped the medicine by the ninth day.

Some patients also tend to deny taking medicines when they have. One study found that 29 of 38 patients who had taken meprobamate, barbiturates, or phenothiazines denied taking these drugs.

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References: 1. Shuman, C.: Am. J. Med. Sci., 225:54, 1953. 2. Perchuk, E., et al.: Angiology, 12:102, 1961. 3. Rawls, W., et al.: Med. Times, 87:818, 1959.

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NEW BOOKS IN REVIEW

HUMAN DEVELOPMENT with 29 Authorities. Edited by Frank Falkner, W. B. Saunders Company, Philadelphia and London, 1966. 644 pages, illustrated. $20.00.

Reviewed by: LOUIS H. NAHUM

The complexity of the problem of human development is well illustrated by the titles of various chapters which range from biologic principles of growth to developmental genetics, perinatal development, physiological growth, developmental aspects of biochemistry, influence of hormones on human development, development of the nervous system, psychological development of the child, cultural patterning of child development, speech, language, hearing, vision, bone, development of immunity and much else. A special bonus is an appendix with an outline of prenatal development and a reference table of correlated human development. Each chapter is written by an outstanding authority and followed by an extensive bibliography.

There is evident in this book a broad sweep of the factors involved and mechanisms operative in human development much of it being based upon recent discoveries in molecular biology, biochemistry and biophysics and biomathematical methods to establish norms. It provides an excellent and indispensable exercise for all people interested in thinking about factors involved in human development. In each chapter is a clear statement about known facts, the limits of our understanding and the need for further work.

With so much information available it was time to collect, collate, codify and evaluate the data that has accumulated. Professor Frank Falkner probably better than any other individual was the one to realize such a task. He himself has done diligent work especially in his study of twins. He has inspired and co-ordinated a whole series of experiments studying the growth of the child. Being himself in such a privileged position, he could observe, analyze and unite with eminent personalities to produce this fine book and he has indeed succeeded admirably.

As it turned out it has provided a practical working tool for Pediatricians, and a base line for active investigators in the field of development. It meets the need of physicians and of basic scientists who will find in special chapters knowledge appropriate to their fields. It will also serve the very extensive ancillary and paramedical services whose work relates to human development, for it is a book that brings many areas together for the first time.

Presumably the problem of organ induction is still too early to be considered in this book and perhaps the role of territoriality in the development of social order will when the principle becomes applicable to human socialization also find its way into the next edition.

One thing that is highly commendable is the beautiful format of a two column page and printing in the highest tradition, for which all the readers of this book will be grateful to W.B. Saunders Company.

DISEASES OF THE HEART. Charles K. Friedberg, M.D., 3rd edition. W. B. Saunders Company, Philadelphia and London, 1966. 1787 pp. $22.00 ($26.00 in 2 volumes).

Reviewed by: LOUIS H. NAHUM

There has been a deluge of new information and ideas in cardiology in the last ten years which has required Doctor Friedberg to bring his last edition up to date. The rapid advances have taken place in instrumental technics in cardiac surgery, in circulatory pharmacology and on a more basic level in structure and function of the various myocardial cells and their relation to the sodium potassium and calcium ions. Any area of progress in cardiology whether it is in instrumentation such as ultrasound echo or selective coronary angiography and radioscan; whether it is in circulatory pharmacology such as new diuretics, new concepts in digitalis toxicity, lysine and arginine to potentiate mercurials, and drugs acting on alpha and beta receptor sites and adrenergic blockers is all here.

Not neglected is the danger recently recognized of using precordial electric shock to treat arrhythmias in patients who are fully or over digitalized. The treatment of cardiac arrest, cardiogenic shock and medical and surgical management is extensive. Reevaluation of anticoagulants; proposed surgical treatment of coronary artery disease, of renovascular hypertension, newer antibiotics in the treatment of bacterial endocarditis, assisted circulation, cardiac grafts and even heart replacement is dealt with.

Obviously this therefore becomes a reference book with a main focus on clinical aspects which is Dr. Friedberg's special area of competence. What is obvious from all this is that the field is now much more formidable to be covered in its entirety by a single individual and in general the trend from now on will be towards books of multiple authorship or books, papers or reviews dealing with a small segment of a field.

Friedberg's book is very large, heavy to handle and difficult to read. Doubtless students and beginners in cardiology will seek lesser works which would be more suitable in a special topic. In the end however because of its comprehensiveness and rational treatment of current points of view, it must be considered encyclopedic and in a class by itself. For there exists now few single individuals that can claim more than a working understanding of material so complex as cardiology has now become. The only one this reviewer knows who has this comprehensive knowledge is Friedberg and probably the last one who can marshal the vast accumulation of complex knowledge in one organized volume as he has.

Some sentences are tortuous such as one on anticoagulants that is about 80 words long. Some treatments are vestiges from the past such as oxygen under pressure in cyanotic patients. There are a few mispelled words such as this reviewer's name in a reference and the first few pages of introduction and table of contents are garbled. However these are unimportant details. What is important is that this is an encyclopedic work of great merit that should be on every physician's desk for constant reference.

ESSENTIALS OF GYNECOLOGY. Author: E. Steward Taylor, M.D. Lea & Febiger, Philadelphia, 1965. Third Edition, Illustrations: 358 black and white and 27 in color on 10 plates, 603 pp. $15.00.

Reviewed by: ORVAN W. HESS

This is the third edition of a textbook in which the author presents the essentials of Gynecology in a lucid manner for the use of students and practitioners. Additional material has been included particularly that which concerns newer knowledge pertaining to normal and abnormal physiology of the female endocrine system, the diagnosis and treatment of infertility, implications of the genetic basis of certain developmental defects of the reproductive organs, and the management of the common stress incontinence. A chapter is devoted to the still incompletely understood problem of dysfunctional uterine bleeding. Of special interest is the chapter which chronologically records the events which have shaped gynecology. In an age when hysterectomy is frequently performed for minor indications to alleviate symptoms and the critical view of tissue committees is sometimes challenged by clinicians, it is a startling revelation that this operation was first successfully performed less than 100 years ago. References in this text book should be of value for all practitioners to supplement observations gleaned from their clinical experiences.

DIURETIC THERAPY — An Appraisal of Diuretic Drugs. Edited by Arthur C. de Graff, M.D. and Alan F. Lyon, M.D. The C. V. Mosby Company, St. Louis, Missouri, 1965. 41 pp $3.50.

Reviewed by: WILLIAM F. ECKHARDT

This slim volume is a reprint of papers which appeared in the American Heart Journal 1964-1965.

My only objection to this monograph is the high cost. Most of the information can be obtained in the new editions of standard texts of pharmacology and cardiology or by reviewing the original volumes of the American Heart Journal. Discussion of the newer, more potent diuretics is too sketchy for this reviewer to recommend this summary.

SYMPOSIUM ON CEREBROVASCULAR DISEASE. American Heart Association Monograph Number 11. Edited by Robert G. Siekert, M.D. From the 38th Scientific Sessions of the American Heart Association. 55 pp. $2.50.

Reviewed by: WILLIAM F. ECKHARDT

Readers of Circulation will be familiar with this monograph which appeared as a supplement to the May 1966 issue. Several interesting studies are reported which should be read in their entirety by interested physicians. The Neurology Section of the Veterans Administration Cooperative Study of Atherosclerosis reported on the failure of long-term estrogenic therapy in small and moderate dosages to reduce the incidence of cerebral or myocardial infarction in 582 men followed for periods up to 34 months. Seymour Eisenberg reported on a significant increase in blood viscosity measured at the bedside or patient with recent cerebral infarction. The remaining papers are of more basic interest and cover diverse topics, cortical potentials in patients with stroke, the use of hyperbaric oxygenation in the treatment of cerebral ischemia, and cerebral hemodynamics during Valsalva maneuver. It is attractively printed but the cost seems a little excessive.

CIBA FOUNDATION COLLOQUIA ON ENDOCRINOLOGY. Volume 15, 1964. Aetiology of Diabetes Mellitus and its Complications. Little, Brown & Company. 395 pp. with illustration.

Reviewed by: WILLIAM F. ECKHARDT

At the present time when drug companies are under fire from government agencies, it is refreshing to find that the Ciba Company has for a number of years supported small conferences and published the results expensively in well printed and illustrated monographs.

This monograph explores the natural history of diabetes mellitus, discusses the pancreatic beta cell, and the biosynthesis and secretion of insulin and discusses insulin antagonism and the role of the pituitary in human diabetes and its complications.

The most interesting sections to this reviewer were Lacy's description of his electron microscopic studies of the pancreatic beta cell and the panel discussion on insulin biosynthesis and secreation of insulin which provide an excellent summary for the basic science interested clinician. All of the Ciba Volumes should be available at Hospital Libraries for the use of house staff and to settle basic science arguments among the clinically oriented visiting staff.

Three cheers for the Ciba Foundation.

MANAGEMENT OF JUVENILE DIABETES MELLITUS. By Howard S. Traisman, M.D. and Alvah L. Newsomb, M.D. The C. V. Mosby Company, St. Louis, Missouri, 1965. 147 pp., with 16 figures including one color plate. $12.75.

Reviewed by: CHARLES A. WOODS

This monograph provides for the first time a concise and complete method of treating the juvenile diabetic. Information of this kind was heretofore found in many isolated journals and books.

Pediatricians and general practitioners are not often called upon to treat a child with diabetes mellitus. Memory of seldom used facts is soon displaced by new thoughts. These 147 pages in your library provides a very quick, thorough and interesting review of this subject.

The contents are divided into eleven chapters. The first seven chapters of the book deal with such subjects as epidemiology, diagnosis, treatment, and instructions to parents and patients. The eighth chapter is concerned with diabetics in infancy. Also is included a discussion of transient diabetes in early infancy. Chapter nine is a potpourri of topics such as oral hypoglycemic agents, idiopathic insulin-resistant and lipoatrophic diabetes, and even information on insurance for diabetics. Chapter ten relates the prognosis of diabetes mellitus. A valuable addition to this monograph is chapter eleven.

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Here is presented a discussion of the infant of a diabetic mother.

A chapter that one might take issue with is chapter seven. The emphasis on diet and its careful composition along with calorie limitation is thought by some to be unnecessary. Many tend to use a more normal diet with a low content of fat. Information on such an approach is lacking. Conservative diet management has a wide acceptance and this should have been made more clear.

Excellent charts and illustrations are numerous for instruction to patients and their parents on the different insulins, care and use of instruments for drug administration and methods for keeping diabetic charts.

A very large appendix gives outline aids on instructions for students on routine nursing care, instructions on collection of specimens for diabetic urine tests, nurses' instructions to parents of the diabetic child, and fluid and electrolyte therapy.

This monograph will be very helpful to the physician caring for a child with diabetes mellitus.

Missile Wounds In Viet Nam

The Viet Nam conflict is presenting new problems in treating the wounds of war, three Army surgeons say in the current Journal of the American Medical Association.

New, high-velocity weapons are causing tissue damage greater than any previous small arms, said Major Norman M. Rich, Major Egon V. Johnson, and Lt. Col. Francis D. Dimond, Jr., of the U.S. Army Medical Corps.

On the other hand, improved medical care is cutting loss of life on the battlefield. Rapid helicopter evacuation, adequate blood replacement, antibiotics, established principles of war surgery, and modern operating room equipment have markedly lowered the Viet Nam statistics for deaths due to wounds, compared to earlier wars.

Weapons as new as the M-16 rifle and as old as the bow and arrow created the hundreds of kinds of wounds seen by the three surgeons at the Second Surgical Hospital in South Viet Nam. This report is on 1,196 patients treated at the hospital in the first five months of 1966, and particularly 521 missile wounds treated in that time.

About half the missile wounds were from gunshots, and about half were due to fragments from grenades, mortars, artillery, mines, etc.

There also were four arrow wounds.

There were 243 wounds from Punji sticks, an ancient, but dangerous weapon of the Viet Cong. A Punji is a sharpened stick with a fire-hardened, contaminated point. It is placed in the ground at an angle designed to puncture a soldier's foot.

In most cases, Punji sticks disable men about as long as would similar small-arms wounds, the surgeons said.

"The Viet Cong have been ingenious in designing booby traps that utilize small-arms ammunition," the surgeons said.

One wooden trap with a simple rubber-band mechanism and a small nail to act as detonator can fire a .50-caliber bullet or a shotgun shell when someone steps on the wire release.

Another simple trap consists of two boards with three .45-caliber bullets imbedded in one of them. Approximately eight pounds of pressure will detonate these bullets when the boards are pushed together by an unsuspecting soldier's foot.

The American M-16 rifle is a very effective weapon, the surgeons point out. Its bullet's high velocity (3,250 feet per second) causes enormous tissue damage. The "tumbling effect" of the bullet after it strikes an object adds to this injury.

The surgeons saw the effectiveness of the M-16 when some of these rifles fell into the hands of Communist forces and were fired at Americans, wounding several.

Only 1.3 per cent of American soldiers wounded by missiles died after operations at the surgical hospital. This is a markedly lower figure than for similar operations in Korea and World War II.

Wound infections after primary wound-closure operations totaled only two per cent.

Of those sustaining missile wounds, 58.1 per cent were returned to duty after an average stay of 16 days in the hospital.

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PLAN NOW AND SAVE THE DATES

Letter To The Editor

To the Editor:

Since I have long been interested in the role of the kidney in hypertension, I read with great personal interest your editorial comments on "Oxygen Sensitive Arteries." In your reporting I believe there may be clues to the etiology of renal hypertension. While there is no mention made of the renal arteries being affected by the rise and fall of P_{CO_2} or P_{O_2}, what occurs in other arteries may equally apply to the renal vessels.

It is more or less accepted that renal ischaemia is a factor in renal hypertension. In a letter I received from Dr. John P. Merrill in May 1966 in reply to my question of oxygen saturation, he stated, "Preliminary observations suggest that renal ischemia caused by mechanical occlusion results in an increase in urine P_{O_2}. The explanation for the latter finding is not entirely clear."

I quote from an article which appeared in the Journal of the A.M.A. Oct. 25, 1965—Vol 194 entitled, "Urinary Oxygen Pressure in Renal Parenchymal and Vascular Disease."—K. O. Leonhardt, M.D. and Ralph R. Landes, M.D. "In severe bilateral renal-artery stenosis, paradoxically, a significantly higher Puo_2 was obtained from the ischemic than from the normal kidney." Their explanation based on the study of the parenchymal Po_2 in normal and diseased kidneys is against the predominant role of the plasma-skimming mechanism.

Quoting the above authors again, they have observed, "that in renal artery stenosis the counter-current exchange of oxygen was, perhaps due to the sudden, ubiquitous ischaemic damage, severely impaired in the inner medulla and papilla while still functioning in the corticomedullary zone." If confirmed, these observations would imply that the Puo_2 in renal artery stenosis reflects the parenchymal Po_2 of the border zone without subsequent exposure to an active counter-current mechanism in the papilla (which is normally responsible for the low Puo_2.

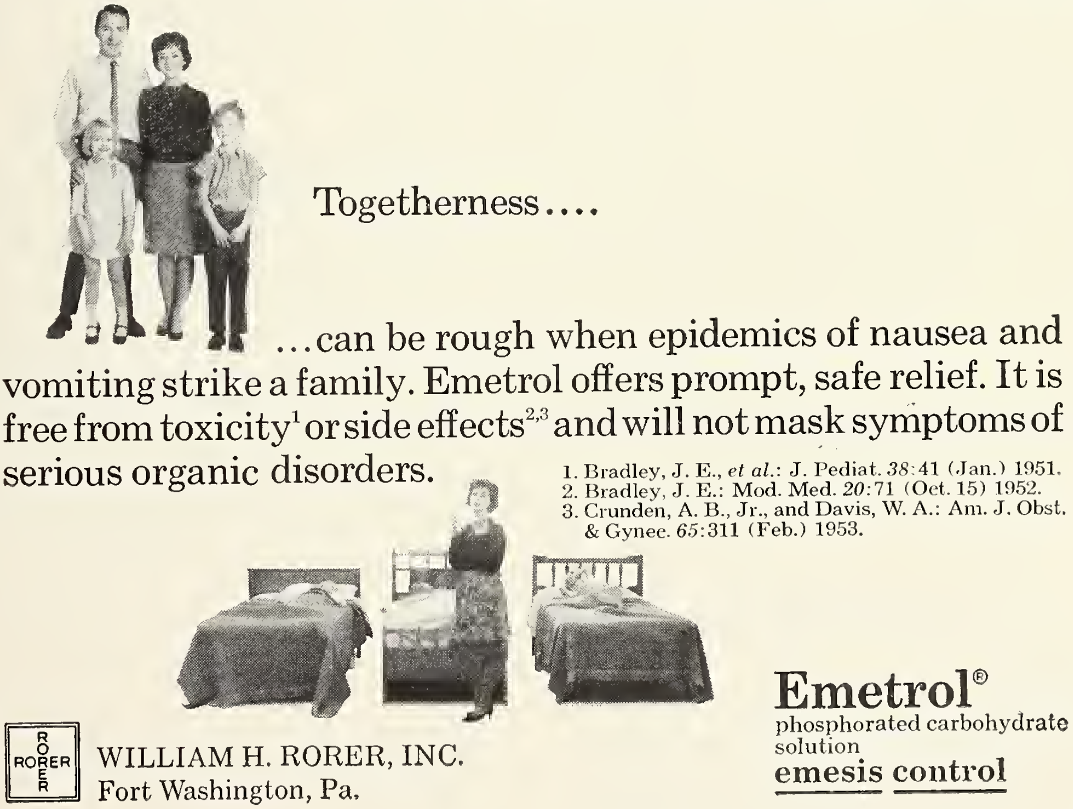
I gather two impressions from your editorial and from the evidence I have brought to your attention. The use of separate urinary Po_2 studies to determine whether or which of the two kidneys or both carries the blame for the existing hypertension seems to be in order. Having determined the existence of these abnormal findings in the urine, one can translate these as originating in a kidney and a better evaluation of the responsibility of existing blood vessel changes for contemplated surgery.

Yours truly,

New Haven, Conn.

H. A. Levin, M. D.

Letters to the Editor are welcome and will be published for informative and educational purposes as space permits. As with other material which is submitted for publication, all letters will be subject to the usual editing. Address all correspondence to: The Editor, Connecticut Medicine, *160 St. Ronan Street, New Haven, Connecticut, 06511.*



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1. Bradley, J. E., *et al.*: J. Pediat. *38*:41 (Jan.) 1951.
2. Bradley, J. E.: Mod. Med. *20*:71 (Oct. 15) 1952.
3. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. *65*:311 (Feb.) 1953.

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1967 MEETINGS

March 30—183rd ANNUAL MEETING of New Haven County Medical Association will be held at Waverly Inn, Cheshire, Connecticut, at 3:30 p.m. Dinner at 7:00 p.m.

April 11—ANNUAL MEETING of the Fairfield County Medical Association. Time and place to be announced.

April 11—ANNUAL MEETING of the Litchfield County Medical Association. Time and place to be announced.

April 12-13—Seminar on Hospital Infections in Connecticut jointly sponsored by Connecticut State Medical Society, Connecticut Hospital Association, Yale Medical School, Connecticut State Department of Health and the Communicable Disease Center of the Public Health Service at Valle's Steak House, Hartford, Connecticut.

April 18—ANNUAL MEETING of the Tolland County Medical Association. Time and place to be announced.

April 19—ANNUAL MEETING of the Hartford County Medical Association will be held at the Hartford-Hilton Hotel, Hartford, Connecticut. The business meeting will begin at 5:00 p.m. with cocktails and dinner to follow at 7:00 p.m.

April 20—ANNUAL MEETING of the Middlesex County Medical Association. Time and place to be announced.

April 25-27—175th ANNUAL MEETING of the Connecticut State Medical Society to be held at the Hartford-Hilton Hotel, Hartford.

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Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage. Make regular blood counts. Discontinue the drug and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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Warning: Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: By May 1963, experience with norethindrone 2 mg.—mestranol 0.1 mg. had extended over 24 months. Through miscalculation, omission or error in taking the recommended dosage of Norinyl, pregnancy may result. If regular menses fail to appear and treatment schedule has not been adhered to, or if patient misses two menstrual periods, possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during period of gestation since virilization of the female fetus has been reported with oral use of progestational agents or estrogen. When lactation is desired, withhold Norinyl until nursing needs are established. Existing uterine fibroids may increase in size. In metabolic or endocrine disorders, careful clinical preevaluation is indicated. A few patients without evidence of hyperthyroidism had elevated serum protein-bound iodine levels, which in the light of present knowledge, does not necessarily imply hyperthyroidism. Protein-bound iodine increased following estrogen administration. Bromsulphalein retention has occurred in up to 25% of patients without evidence of hepatic dysfunction. Studies from 24-hour urine collections have shown an increase in aldosterone and 17-ketosteroids and decrease in 17-hydroxycorticoid levels. Thus, Norinyl should be discontinued prior to and during thyroid, liver or adrenal function tests. Because progestational agents may cause fluid retention, conditions such as epilepsy, migraine and asthma require careful observation. Thus far no deleterious effect on pituitary, ovarian or adrenal function has been noted; however, long-range possible effect on these and other organs must await more prolonged observation. Norinyl should be used with caution in patients with bone, renal or any disease involving calcium or phosphorus metabolism.

Side Effects: Intermenstrual bleeding; amenorrhea; symptoms resembling early pregnancy, such as nausea, breast engorgement or enlargement, chloasma and minor degree of fluid retention (if these should occur and patient has not strictly adhered to medication plan, she should be tested for pregnancy); weight gain; subjective complaints such as headache, dizziness, nervousness, irritability; in a few patients libido was increased. In a total of 3,090 patients, 2.2% discontinued medication because of nausea.

NOTE: See sections on contraindications and precautions for possible side effects on other organ systems.

Dosage and Administration: One Norinyl tablet orally for 20 days, commencing on day 5 through and including day 24 of the menstrual cycle. (Day 1 is the first day of menstrual bleeding.)

Availability: Dispensers of 20 and 60 tablets; bottles of 100.

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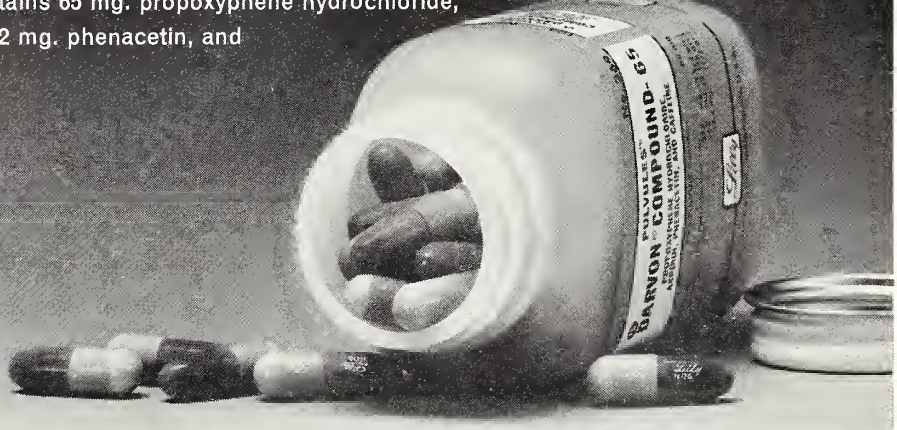

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editorials

An Attempt To Deter The Nation's Paramount Public Health Problem: The Anti-Coronary Club

The hypothesis had been proposed that a diet that will result in a lowering of serum cholesterol will lead to a decrease of the incidence of Coronary Heart disease (CHD). Accordingly a project was started in 1957 by the Bureau of Nutrition of the New York City Department of Health in which a group of 814 men at large, age 40-59 had been placed on a diet relatively rich in polyunsaturated fatty acids, lowered calories, and lowered sodium—the "prudent diet."[1]

The subjects came every 5 weeks for venipuncture and serum cholesterol determinations as well as consultation with a nutritionist. Every 10 weeks the subjects had a clinical and nutrition review session by a panel of physicians and every year a medical history with physical examination, laboratory data, electrocardiogram and roentgenogram. The clinical and electrocardiographic criteria of the New York Heart Association were used to establish new and old coronary events.

Adherence to the "prudent diet" significantly lowered serum cholesterol levels. There was a progressive increase in the per cent of linolenic acid in the fat depots of the subjects. We must remember that linolenic acid is an essential unsaturated fatty acid which is commonly derived from dietary sources and has been proposed as a factor that reduces platelet adhensiveness and therefore arterial thrombosis.[2] Further investigation by Christakis *et al* have shown that the experimental diet did not lower either Vitamin A or E in their subjects and that long term adherence to the study diet did not demonstrably increase serum triglyceride values.

The comforting findings were a sharp reduction of a coronary event in the experimental group as compared to their control group. In fact there occurred three times as many incidents in the control group as in the study group. Those who adhered to the program of diet and supervision by frequent interviews gave evidence of their adherence by an increase in linolenic acid in their fat depots as well as a significant decrease in serum cholesterol during the first year of active status in the "Club" and remained so throughout the study.

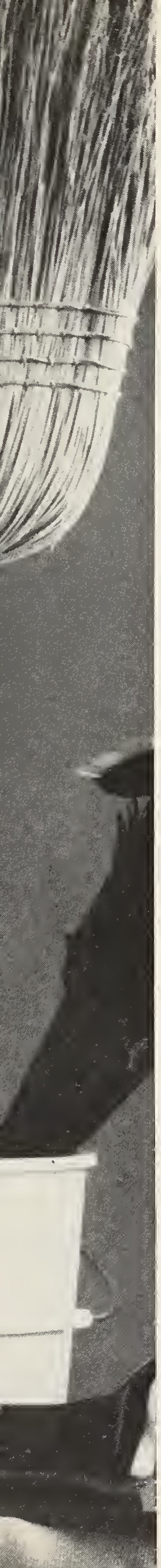
Many important questions relevant to the effects of the Anti-Coronary Club program still await final answers. The number of new coronary events through the end of the period of observation is small and a follow-up of both controls and members of the club must continue. One problem is whether the low incidence rate in the experimental group will be maintained as participation continues. Another question is whether among the new events that may occur in this group they can be related to characteristics other than the diet and in what proportion.

The prospective Framingham study[3] has confirmed that an association exists between the incidence of CHD and the presence of such "risk" factors as obesity, hypertension, hypercholesterolemia and cigarette smoking. The identification of such risk factors constitute a major advance in the effort to control the public health problem posed by CHD. It is not unreasonable then to attempt to control CHD morbidity and mortality by attacking these associated conditions.

Christakis study diet was effective in lowering the serum cholesterol levels in their middle-aged subjects and in maintaining lowered levels for periods as long as five years. The diet also was effective in reducing obesity and hypertension in the participants, a fact not found in the control groups. A consequence of reducing these risk-factors showed itself after four years in a significant decline in morbidity from CHD.

This study confirmed what we already know in general about the relationship between diet, hypercholesterolemia, obesity and hypertension. When the fatty acid intake is mostly unsaturated and especially containing linolenic acid, the serum cholesterol levels will decline after a long period. Low caloric intake prudently undertaken can be unusually successful in reducing weight of obese subjects and maintaining normal weights. The diet was also low in sodium and this may account for a decline in arterial pressure levels in these subjects. Then of course was the psychologic factor of commitment to a cause, enforced and reinforced by intense nutritional guidance the members of the "Club" received.

The practicing physician can use this experience to engage in preventive medicine in his own office. He can use serum cholesterol determinations, and detect other risk factors already established in an effort to reverse these risk factors affecting his



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Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

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patients. Although the decrease in morbidity experienced by Christakis experimental group could not be attributed to cigarette smoking since this factor was not controlled it is important to remember that eliminating smoking also tends to reduce the incidence of CHD.[4] Furthermore we must extend our efforts to reduce other risk factors as well as amelioration of psychic stress and lack of physical activity, since such efforts could well contribute further to the control of CHD.

The AMA[5] has recognized the importance of controlling the level of serum cholesterol in high risk groups and has also suggested the need to control the risk represented by high serum cholesterol levels in the young adult. It has repeatedly emphasized the preventive role of diets that lower the serum cholesterol concentration and has recently taken the position[6] that appropriate dietary changes for the public in general should be considered though this is an extremely complicated and difficult undertaking.

If the results described above are confirmed by other prospective studies on the relationship between diet and heart disease now in progress, there is reason to hope that progress can be made in deterring the nations paramount public health problem.

L.H.N.

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Territoriality And Social Order

Individuals and groups of individuals seem to require a certain amount of space in which to establish and maintain a comfortable social order. This territoriality has been observed in all vertebrates from fish to man and has proved to be a very powerful determinant of social order.

To study territorality, a biologist[1] introduced into a Caribbean island several hundred rhesus monkeys. He furnished adequate food but otherwise their social order was totally disorganized. After a year a steady state was reached, the island had been divided up into discrete areas in each of which was a single group of monkeys. Each group established a comfortable social order of its own which functioned under male leaders who were responsible for most of the initiative and aggressive activity in the colony.

Between the groups in the various domains there was a chronic struggle to maintain the borders of their territory. When one or more monkeys from another domain intruded, it was the signal for a powerful call to social action and the defense of the territory took precedence over any other activity in the colony including sexual activity. Numbers of the group would rush to the frontiers shouting and screaming at the intruders to return home. Occasionally an invading group came relatively close to the heartland of the defending monkeys when the defenders would react with such intensity of activity that the intruders were thrown back. This observation suggests that the enormous emotional tension generated in human affairs by conflicts over territory must have the deepest biological significance. We need however to question seriously whether the human species needs to express its territoriality in this mode.

Symbolic expressions of territoriality are much pleasanter. The monkeys have it in their ritual dance. Ours is played out each week and during the fall season on thousands of gridirons in the country. Remember how easily the ball moves in midfield and how much additional strength there comes to the defenders when their backs are to the goal posts. The howls and shrieks of the monkeys do not kill. This cannot be said of the human who in small conflicts uses zip guns and switch blade knives and in large conflicts, powerfully destructive bombs and much worse.

Vaughn[2] emphasizes the probability that a subtle interplay between forces perceived at one time as imprinting and perhaps at another as territoriality may have a great deal to do with the ultimate capacity of the human animal, for identification with and separation from his fellows; for his capacity for loving and sharing and altruistic and even sacrificial behavior.

In some birds it is the family which establishes the most conspicuous territorial claim. In some migratory birds the male flies ahead to establish territory and sings not a song of love but a cry to others to stay off his property. When the female arrives and housekeeping begins, the cry ends. In some species certain limits of personal territory are very accurately measured, as in the diameter of a circle that pigeons will not invade around a stroller on the boardwalk of Atlantic City. In a similar way different groups of contemporary

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people have established the distance to which they will allow other people to approach without feeling uncomfortable. The Latin will embrace, the North American is standoffish. Turks will hold each others hands as they converse.

Vaughn points out that these phenomena are biologic in birds but could be habitual and susceptible of modification in humans. One of the striking effects of LSD is its tendency to abolish the "touch taboo" and to free the group, interacting under the influence of the drug, for relationships which are perceived by them for this and perhaps other reasons as having entirely new dimensions.

There are many animals who kill members of their own species only where population pressures exceed certain levels. It remains to be learned what profound and compelling biologic effects, in the sense of imprinting and territorial pressures, that human animals undergo when they become ever more tightly packed into cities. We hear of the appearance of a new "adolescent culture" in the western world. How much does it reflect a movement away from the tradition oriented, parent-child, family centered social structure, towards social organization less rooted in the past and more responsive to pressures arising in contemporary life from the crowded cities.

The insistence of the individual and family upon a certain degree of privacy could be one aspect of territoriality. Clearly the need for privacy may be particularly intense in a society such as ours where much of the earth's surface is "owned" by those who occupy it. Bitter and violent altercation arise between neighbors over property lines that separate their two areas of privacy. Our western culture has long recognized the need for and right to privacy. This is how a man's home has come to be his castle which may not be breached unless a warrant offers explicit evidence that the public need is involved. Territoriality however has needed explicit public definition. In our day the privacy of an individual is held not to extend to the place where he offers goods and services to the public, the public properly having access to such places without respect to race, creed or color.

If we recognize the concept of individual privacy and group territoriality it should help us to find proper solutions to many human problems. This implies planning for a human society that would become mature and stable in which national identities and anxieties as well as international tensions will not continue to be a threat to survival. We could learn a lot from birds in whose society, the family and its nest and a circumscribed space constitute both the basic social unit and the territory in which the primal need for space can be realized. Animals generally do not covet each others territory or property and do not practice war as do units of the human society.

Do these new biologic insights help us to some kind of action which will lead us towards a world of peace? They do help us to understand that many of our preconceptions are not a consequence of the natural condition of man. Human slavery accepted for 300 years is now rejected as a natural condition, so is a society segregated to race. Poverty is also not a natural condition of man no more than slavery or segregation. Many have long assumed that poverty was due to some kind of hereditary deficiency in intellectual and emotional capacity. May it not actually represent profound disturbances in the level of stimulation and the quality of socialization of the infant born to poverty in one generation who grows up to recreate his deficiencies in another.

We physicians have a dual role. We must encourage relationships between parents and infants so as to make maximum use of socialization processes. We must seek for means to control or sublimate the emotional energy now wasted on meaningless and destructive anxieties and struggles which may perhaps have elements of primitive territoriality at their roots. To achieve this we must become really concerned with the raising of children capable of effective social action and interaction. We must be knowledgeable in matters bearing on the healthy socialization of children and we must keep abreast of new information and insights.

L.H.N.

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New Light On The Role Of The Nervous System In The Control Of Peripheral Cell Function

A peripheral nerve is far away from its neuron. How does it stay alive, is its function a purely electrical one to transmit impulses? The neurohormones delivered at the nerve cell junction come from where? If from the neuron, what mechanisms are involved in the transfer? Are these substances from the central nervous system capable of passing over membranes and enter into intimate metabolism and function of the innervated cell?

These questions are raised because of many diverse phenomena that are coming to be recognized as intimately related to nerve activity. Trophic influences, influences upon metabolism, function and development, differentiation of cells in embryogenesis, growth and regeneration of the structures they innervate.[1]

We know that when nerve fibers are separated from their cell bodies and there is interruption of exoplasmic continuity, a phenomenon termed Wallerian degeneration occurs. After an interval that varies with length of the distal stump, degeneration or other trophic changes begin in the muscle or other cells innervated by the interrupted fibers. These changes are clearly distinguished from those induced by interruption of the impulses alone.[2,3]

The degeneration of the distal part of the interrupted axon clearly means that the axon all along its length is supplied with components from its neuron that are used for its maintenance and activity, components that are not supplied by other sources such as blood or other extra cellular fluids and schwan cells or by synthesis within the axon itself. If the components that keep the axon alive are derived from its neuron, it must mean that maintenance of the integrity of axons in peripheral nerves depends on the continual delivery of fresh cytoplasm elaborated within the cell body. This cytoplasm must now be propelled in some manner, probably peristaltic, by the axon along its entire length and all its branches replenishing the neuroplasm.

That this is a very active process may be discerned from the fact that the total volume of neuroplasm may be replaced several times each day.[2] If this process goes on in the central as well as the peripheral nervous system, we begin to understand why the brain is such an actively metabolizing organ and why brief interruption of its oxygen supply causes rapid unconsciousness.

Korr *et al*[4] have tested the hypothesis that the trophic dependence of a cell on its innervation is, as in the case of the axon, also based upon continual delivery by the axon of substances that originate in the nerve cell. To do this they applied labelled P_{32} inorganic phosphate or C_{14} amino acid precursors of protein directly to the posterior tip of the floor of the fourth ventricle in 15 rabbits. These are the locations of the neurons from which the hypoglossal and vagus nerves originate. The solutions were deposited in appropriate portions at ten to twenty minute intervals.

As careful investigators they assured themselves that good absorption occurred and that contamination of the cerebrospinal fluid had been avoided. A total of fifty to one hundred mc. were applied in each animal to the nerve nuclei in this manner. The authors first determined that there was no diffuse labelling and that only the vagus and hypoglossal nerves were radioactive. This radioactivity in the form of an irregularly shaped wave front, as observed in a three dimensional scan, advanced along vagal and hypoglossal trunks at about 5 to 5.5 mm. per day. This is consistent with findings in other nerves and in rate of regeneration of the vagus nerve.[3]

The radioactivity reached the tongue through its hypoglossal nerve after about five days and the cardiac atria through vagus nerve after about nine to ten days. If one hypoglossal nerve was crushed, the radioactive material was arrested at the site of nerve interruption where it accumulated. In the uninterrupted hypoglossal nerve the radioactive material progressed to the cells in the tongue innervated by the nerve.

Having shown that radioactive material had been transported only by the intact nerve, the next obvious step was to determine how the material was distributed in the muscle cells of the tongue that are innervated by the hypoglossal nerve. This they accomplished with micro autoradiographic techniques. They found that the radioactive particles were densely packed in the trunk of the hypoglossal nerve but not in its sheath. In time the labelled molecules were distributed throughout the proximal muscle cells of the tongue in the vicinity of the entry of the nerve. The particles were not just at the myoneural junction, but in the fibers, nuclei and sarcoplasm. All other cells in the tongue such as connective tissue, blood vessels, lymph channels showed no labelling with radioactive particles. Neither did other nerves distributed to the tongue such as the facial trigeminal glossopharyngeal and sympathetics.

It is clear that when radioactive substances, precursors of protein synthesis were selectively introduced into hypoglossal neurons, these substances or their derivatives were conveyed down by axons only to the muscle cells of the tongue, that they reached the muscle cells only via these axons. Finally the labelled molecules did not remain at the neuromuscular junction but penetrated into the intracellular components of the muscle cells.

We see here a clear design in which there is proximo-distal conveyance and intracellular transfer of substances from the neuron to peripheral cells. Not just electrical impulses, not just deposition of neurohumors at nerve cell junction, but actual transfer of material manufactured in the neuron to the cytoplasmic materials inside the innervated cell.

What can the function of these materials be? Can they underlie the so-called trophic and other long term influences, not based on electrical impulses, of peripheral neurons on the metabolism function, development, differentiation, growth and

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regeneration of the structures they innervate? If they do, how do they accomplish this?

This kind of work has opened a new dimension in the role of the nervous system in peripheral cell function.

L.H.N.

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Differentiation During Embryogenesis. The Role Of Induction

Years ago there raged a controversy between the concepts of preformation and epigenesis. The preformationists held that if we could actually see the structure of the fertilized cell magnified enough there would emerge in miniature the individual that results from oogenesis. Those who held for epigenesis, insisted this was pure imagination and only a developmental process finally leads to organogenesis found in the infant at birth. As was true with other antitheses in biology, argument without facts were pure fantasy, and that as knowledge progressed it led to a synthesis of opposing views resulting in elimination of the antithesis.

All events in embryogenesis of course begins with oogenesis and the difference between embryos is determined here and this must be due to regional differences in egg cytoplasm from which future cells are derived. These early determinative effects are now referred to as predetermination not preformation. For soon after fertilization, special regions of the egg are incorporated into the cells cleaving from that region of the cytoplasm and impart to them the ability to induce the main axial organs.

As development proceeds, the cells of a multicellular organ become differentiated one from another although they are all endowed with identical genomes. Obviously a second mechanism is here involved besides predetermination, this is termed Embryonic Induction, an interaction between one tissue the inductor and another responding tissue. As a result the responding tissue now takes a course it would not have followed had the interaction not occurred. In each developing organ the induction begins at different times and ends at different times. We are beginning to understand what induces what. We do not yet know what the inductor substances are.

Up to the present time most studies of embryonic induction have been carried out on amphibians. In the salamander, the ectoderm is the most dependent on induction, for the emergence of the various organs it forms. The central nervous system is the first set of ectodermal organs to appear and the responsible tissue is the chorda mesoderm. As the nervous system develops it in turn participates as an inductor in the determination of other ectodermal organs including the nose, lens and ear.

The central nervous system is one of the most strongly predetermined of the ectodermal derivatives and requires the least subsequent inductions. This induction system can be brought into operation by any number of odd treatments or substances and this has made extremely difficult an understanding of this induction system.

The nasal sac, the lens of the eye and inner ear structure are far more amenable subjects for study of embryonic induction than the nervous system. They are less predetermined, are relatively simple discrete organs. Jacobson who has studied lens induction exclusively has found three different inductor tissues in the ectoderm that induces the lens and has carried his observations from the first visible sign that a lens is forming until it has been finally completed. This story he achieved from explantation experiments. The remarkable part of this work is to show that any part of the early ectoderm can form a lens if sufficiently exposed to lens inducing tissues.

Another important question is what fixes the organ site since all organs of the body are strictly limited to a particular site if they are to have well-adapted functional integration with the rest of the organism. Jacobson points out that the solution of the problem of what fixes organ site must finally come from investigation of events that occur during oogenesis and at, and shortly after fertilization, the events that establish predetermination. This is a monumental task for descriptive chemical embryology but should not take too long for answers.

Another question is what brings inductor and reacting tissue together in quite a precise fashion under normal conditions. We need such knowledge to account for the site of determination. The first sign in the induction of the lens in a chick embryo is a change in the behavior of the reacting cells, involving their shape, clumping, elongation of cell oriented microtubules. The whole process is extremely complicated, but in most instances continued presence of the inductor tissue is necessary for maintaining and augmenting the new associations in developing organs.

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During early development any region of the epidermis of the head is simultaneously being induced to become nose, lens, and ear for example. A level of determination for each of these organs is discernible in any region of the head epidermis in the neurula stage. The nose, lens, and ear form from the strip of epidermis that is just lateral to the anterior neural folds. If you remove this strip and rotate it 180° it is possible to form both noses and ears anteriorly as well as posteriorly.

Varying such delicate embryologic surgery has revealed the role of epidermis, endodermal and mesodermal inductors to fix the sites of nose and ears and lens. An understanding of a spatial and temporal organization of an induction process is necessary for the interpretation of ultrastructural findings. Ultimately a synthesis between chemical knowledge of the inductor substances as well as knowledge of their results in embryogenesis will finally explain organogenesis. In the meanwhile studies of the induction systems in their organized states will continue to provide new information about the role of induction in cell differentiation.

L.H.N.

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Cooperation Between Law And Psychiatry. Treatment—Not Punishment

A more fundamental attack on the crime problem is nowadays called for, based on a theory more promising of protection of society through rehabilitation of offenders than is the hallowed basic philosophy of traditional Criminal law.[1]

In 1952 The Civic Center Clinic of Brooklyn was founded as a result of astute cooperation between a District Attorney and the Courts in order to bring the technics and insights of the social sciences in the interests of "far-reaching" justice. Judge Edward S. Silver then District Attorney, was appalled by the futility of arraigning the same offenders time after time, and so he decided that there must be a better answer to crime than just sending men to prison. With a group of professional men and community leaders he organized a small clinic to which offenders could be referred by the prosecutor and the courts for appraisal and rudimentary therapy. The clinic with official, philanthropic, and popular support has grown to imposing proportions and under the eyes of the present D. A. Aaron A. Koota, it has become an important community asset.[2]

Offenders of nearly all types but with preference to young and early offenders are referred to the clinic by the D.A. or by the court. In the clinic, which is now under the auspicies of the Community Mental Health Board of New York, medical, psychological, psychiatric and social service personnel cooperate in the examination, appraisal, and prognosis in each case. They meet in a group conference to evaluate the offender and carefully weigh the possibility of retrieving him from a life of crime. The procedures include the use of drugs, individual or group psychotherapy or both, practical counseling and in fact any resource that seems appropriate and promising. The clinic has dealt with sex offenders, perpetrators of aggressive crimes such as hold-ups and also users and pedlars of narcotics.

This type of medically oriented accessory of the bench can operate in many ways to advise and assist the judge and carry out the court's considered prescription for the offender. It can provide for the trial an important background on the personality and condition of the defendent and the significance of his behavior and environment. Finally it can and is equipped to pursue under the Court's direction the treatment and supervision of persons found worthy of a rehabilitative program. Experience with these procedures is constantly improving their effectiveness and broadening the range of their application.

Ten years ago a similar program to provide psychiatric services to courts was also established in Massachusetts. From a small beginning of one pilot clinic the system now operates fifteen clinics in Courts throughout the state.[3] The services that have been developed are two fold, the first being a consultative function to give opinions in matters of competency, mental hospital commitment, dangerousness, disposition and possibility of treatment. This is an extension of the role of psychiatry in the courts and serves to help resolve the numerous questions relating to the mental condition of the accused.

Russell holds that the psychiatrist belongs in the system of justice not after conviction but from the time of arrest through to the disposition. His experience is clear that a psychiatrist can render valuable assistance to the legal process and that the court clinic is among the most effective means of rendering this service. When a man commits a crime and has a mental illness which prevents him from understanding who or where he is or why he is there he ought not be made to stand trial for the offense. The psychiatrist is able to assist in the determination of these issues as well as to help salvage whatever future remains to the accused. The issue of who shall be hospitalized against his will

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and the assessment of dangerousness will surely require close cooperation between Law and Psychiatry.

The successful clinic is in the role of amicus curiae, a member of the court family and has prompted one judge to remark ". . . . . my effectiveness and the effectiveness of my court would be greatly impaired if it were not for the court clinic." A second service offered by the Massachusetts court clinic, as in New York, is the treatment of the offender and it is this pervasive interest in offender rehabilitation that makes the program unique in its operation. The Massachusetts clinic system has become in ten years the largest system in the country for the outpatient psychiatric treatment of the offenders and it is this aspect of the work that offers a great challenge with great rewards.

The reasons for treating offenders rather than punishing them is based upon a modern approach to aberrant behavior. In many cases an offense of delinquency is a sign or symptom of an underlying social or emotional problem. Furthermore, such offenders because of defect in character structure can be most effectively treated in the court probation clinic setting.

The fifteen clinics are currently staffed by forty psychiatrists, ten of whom are training fellows, ten social workers, seven social work students and four consultant psychologists and a liaison agent. The overall figures indicate that more than fifty per cent of clinic time is actually spent on the treatment of the offender. A principal focus of the clinic, Russell points out, is on the level of probation, aiding the probation officer in his investigation of cases and in his work of rehabilitation of offenders. Probation clinical case conferences are regularly scheduled for presentation and discussion of individual cases by the whole assembly of special talent. The conferences involve therefore the total impact of the community and have served a coordinating function as well as being of educational value for all the disciplines involved.

The program is extensively used as an affiliated training facility for psychiatric residents, for child psychiatry fellows for legal-psychiatry, fellows of the Law-Medicine Institute and as field placement for students of social work schools. The direction for progress will be in the development of more complete services to the Court System through regionalizing of clinics, in the development of new modalities for the rehabilitation of offenders and certainly in more intensive investigation and research.

In Connecticut we have yet to take the first step. Here if the court so orders, a person is examined by a psychiatrist.[4] Because the philosophy of psychiatry is so different from that of penal institutions one may anticipate reluctance on the part of Psychiatry to deal with offenders in a setting devoted to punishment. There is an institution in the planning stage where the courts will be able to send offenders for examination and treatment and even probation, but only for those who commit crimes punishable at the States Prison, meaning those with at least one year sentence. There is hope, for as we have seen above modern scientific and social enlightenment is having its impact on correctional idealogy. We are thinking of treatment not punishment, of means to turning a "human waywardness towards rectitude. "

L.H.N.

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Fluoride Protection Of Bones And Teeth

The fluoridation of water supplies to furnish drinking water that can effectively prevent dental caries is no longer in question. However the potential benefits of ingested fluoride in the management of various general illnesses notably metabolic bone diseases has also assumed importance and many basic science and clinical studies are underway to help establish a rational basis for such therapy.

First of all is the evidence which comes from tissue culture studies. Cellular reproductivity seems not to be affected when the cells are exposed to 5-10 parts of fluoride ion per million. The person who drinks fluoridated water of one part per million has his cells exposed to 1/10 of this amount and then for but a short time as will be seen below. To produce any effect on He La cells Sognnaes[1] points out requires fluoride concentration 30-50 times the concentration ordinarily found in human body fluids. The specialized cell (ametoblasts) that form the dental enamel in children appear to be a little more sensitive to fluoride than He La cells, but this is probably due to a mechanism the enamel organ possesses for local concentration of the fluoride salt.

One remarkable aspect of fluoride ingestion and metabolism is the curious fact that it is almost impossible to raise markedly the fluoride level in blood plasma in logical relation to oral ingestion of flouride even at extremely high concentration.

Regardless of what fluoride dosages have been given to animals and man they maintain a markedly constant plasma level of fluoride. Doubling the amount of fluoride recommended to prevent dental caries produces no increase in fluoride plasma levels.

The body accomplishes this through the kidney and the skeleton. The kidney operates as an extremely efficient organ of fluoride excretion. The soft tissues lose nearly all fluoride within four hours after ingestion. Even after one hour only 10 percent of ingested fluoride is retained in plasma. The part not excreted is then retained by the skeleton so that the target organ after fluoride ingestion is the skeleton including the teeth. In patients deliberately given enormous doses of fluoride such as 50-100 times the normal intake, the kidneys excrete more than half of ingested fluoride and a lesser amount is deposited in the bone crystals in a biophysical process leading to large inorganic crystals of more perfect structure than is found in persons with metabolic bone disease. Obviously if fluoride is deposited in bone and produces more perfect bone crystals, the inevitable question is what would fluoride ingestion do to the bone of patients suffering from bone resorption as is found in osteoporosis, Paget's disease, osteogenesis imperfecta and post-menopausal bone defects.

This subject has been studied in patients who have ingested large amounts of naturally occuring fluoride as well as in patients who have been given high dosages of fluorides in the treatment of bone diseases. Sognnaes points out that all early studies were inconclusive therapeutically because the dosages were either administered for too short a period or were not high enough.

A population ingesting relatively large amounts of naturally occurring fluoride from domestic water containing eight parts per million were studied roentgenologically and received a clean bill of health. Furthermore skeletal growth of the forepaws of young rats was not affected by concentrations as high as 10-20 parts per million. Not only was growing bone not damaged by high concentrations of fluoride ingestion but old osteoparotic bone was beneficially influenced in those populations ingesting relatively large amounts of naturally occurring fluoride in domestic water.[2]

An excellent study to determine the possible microscopic damage of organs, tissues and cells was carried out on cancer patients who were given 80-400 mg. fluoride per day for 4-6 months (320 times amount recommended for water fluoridation).[3] These investigators found no demonstrable damage in post-mortem examinations of tissues. On the other hand benefits have been repeatedly reported after the use of fluorides in people suffering from disturbances in calcium metabolism and various destruction bone diseases of the skeleton. Purves[2] gave 16 patients with Paget's disease 60 mg. of fluoride per day for 2-3 months and a total dose of 20 mg. per day up to one year. Within 4-6 weeks, 14 of the patients gained substantial relief from their bone pain and concommitant disability. Six also showed improvement in calcium retention.

This approach to bone protection has led to elaborate observations on the general metabolic effects, biochemical changes and calcium balance. No clinical symptoms or biochemical evidence of toxic effects was found in any patient receiving fluoride. Fluoride is thought to increase calcium retention as was shown by bone biopsies and calcium 47 studies on increase in bone accretion after the administration of calcium. The conclusion reached was that "fluoride is the only known agent suitable for prolonged administration to humans for the purpose of increasing the density of the skeleton."

Purves' findings have been amply confirmed by Bernstein[3] who found no toxic or systemic effects on any organ system in patients who ingested 40-75 mg. fluoride per day. On the contrary, the treated patients showed by X-ray diffraction that fluoride therapy had resulted in the formation of strong bone.

Sognnaes points out that in dentistry we are faced with severe locallized alveolar jawbone destruction which in the adult population is now leading to greater loss of teeth than is caused by dental caries. Against this process of bone resorption we have very little to offer in the way of prophylactic and therapeutic measures. Accordingly he urges intensive investigation of dosages of fluoride and methods of its local application, since the possibility already exists that bones and teeth can be protected through the administration of fluorides.

It seems fitting also to anticipate the potential need for some special protection of skeletal tissue during periods of immobilization, one type of which is bound to occur during the weightlessness of prolonged space travel. During immobilization, there is bone loss, elevated concentrations of calcium in urine and blood. The hibernating animal is one such experiment in nature. Such an animal is immobile and is undergoing nutritional and other metabolic changes. Interestingly enough, what is especially significant to the dentist, not only do such animals exhibit extensive skeletal bone loss, but also alveolar jawbone loss surrounding the teeth.[1]

We still do not know the maximum fluoride levels that can be tolerated by human tissues. This knowledge might be important if one wishes to treat teeth and bone by local injection of fluoride. What is clear in the development of our knowledge about fluoride metabolism is that dosages used have not led to any recognizable tissue injury. On the contrary it has opened the possibility of protecting the skeleton and teeth by medication and by fluoride even in anticipation of bone loss accompanying incipient or predictable changes in the internal metabolism, as at the menopause, or during immobilization. In fact we already have enough knowledge to state that dosages of fluoride above one part per million level may have new preventive and therapeutic applications for adult individuals suffering from common skeletal and dento-alveolar jawbone disorders of obscure etiology.

L.H.N.

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Science Tools: 20.
The Ballistocardiograph (BCG)

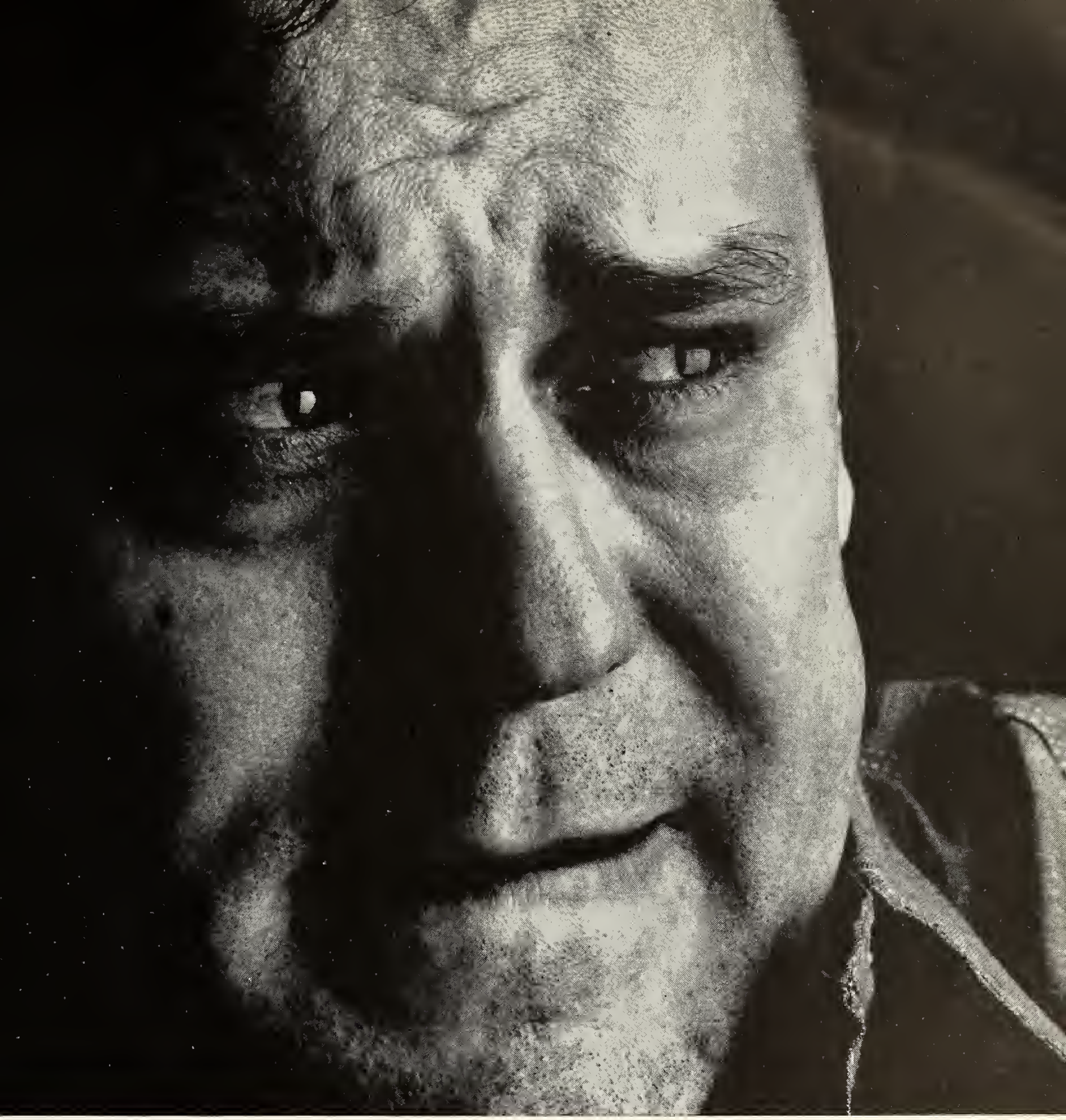
The concept that a sudden motion of the blood imparted to it by the heart in one direction must produce a recoil of the body in the opposite direction is not a new one. Yandell Henderson,[1] a professor of physiology at Yale suspended a table from the ceiling, rested a patient upon it's surface and recorded the movements along the longitudinal axis. The changing velocity of the moving blood within the circulatory system caused the table to oscillate during each successive cardiac cycle.

The blood however does not leave the system and the recoil of the heart and body from ejection of the blood into the arteries is quite complex because actually, the blood ejected from the two ventricles moves simultaneously in several directions. There were other complicating factors originally such as the coupling between the body and the table. Then it developed that the elasticity of the skin acts as a spring interposed between the moving body and the table top and this may profoundly influence the recorded deflection.

Starr[2] extended Henderson's observations and after much improvement in the instrument and experiments both on dogs and human cadavers showed that the size of the initial deflection is determined by the rate at which the velocity of ejection is built up, more than it is by the stroke volume. With the original high frequency apparatus, the size and shape of the deflections are determined almost completely by the elastic properties of the skin, which must be considered as a coupling between the body and the table. For this reason Starr moved to employ a critically damped ballistocardiographic (BCG) apparatus with very low frequency (1.5 cps.) which produces a much more reliable record. And when the BCG is recorded simultaneously with the first derivative of the carotid pulse, one can also recognize right and left ventricular components much more readily.

The obvious limitations of the method, not the least of which is the mass of the body itself, which interferes with recording rapid oscillations, do not preclude the recognition of empirical relationships between various types of cardiac dysfunction and characteristic patterns. Since the amplitude of the deflection is influenced by the rate at which blood is accelerated, variations in the pattern should reveal alterations in the force of ventricular ejection. All of us are profoundly interested in the strengths or weaknesses of the hearts of our patients and in the coordination and incoordination of the cardiac contractions. If the force of ventricular ejection can be recorded and alterations recognized in the BCG, then we are well on the way to an important measurement of the physiologic behavior of the heart.

The older cardiologists like Mackenzie and Lewis never ceased to emphasize the importance of the muscular function of the heart. They attempted to estimate cardiac strength from the pulse, the intensity of the heart sounds, the venous pressure and these were a necessary part of every physical examination. Then came a period when interest in the electrocardiogram increased and interest in the heart as a muscle declined. The ECG informs us only indirectly about myocardial function. It helps to identify some anatomical lesions and occasionally angina pectoris. A study of heart sounds also helps to identify valvular lesions and at times a fatigued heart. No one can deny the great importance of identifying anatomical lesions of the heart. The BCG adds little to our knowledge in diagnosing anatomical lesions for its chief aim is to reveal the changes in the force of heart contraction, the myocardial abnormalities as distinct from the structural changes. Accordingly the chief aim of BCG has been the accurate measurements of the forces of the circulation and the discovery of the clinical significance of such measurements. We accordingly need to understand the normal form and from clinical pathological correlations as well as experiments on animals and cadavers we have come to understand the abnormal forms and assess their diagnostic and prognostic significance.



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The normal form is extremely well documented. In fact there is hardly any clinical method whose genesis is as well documented as that of the BCG. To elucidate all of the numerous abnormal forms, Starr has constructed an electrical model of the circulation which may provide answers to many questions. Thus he has altered the "cardiac ejection curve" and produced specific changes in the form and amplitude of the "force record". When he simulated the condition of atherosclerosis the force BCG did not get smaller but somewhat larger. These modifications also appeared in experiments on cadavers. Thus changes in acceleration of ejected blood are easily recognized in the force BCG.

Starr has also carried out experiments on unanesthetized trained dogs whose BCG looks exactly like that of the human record. In the living animal he could study effects of anesthesia, injection of adrenalin, effects of quinidine, pitressin, hemorrhage, ligation of great vessels, emboli to head and to the lungs. The experiments on animals have agreed perfectly with observations made in the clinic and with theoretical considerations. These experiments to elucidate the meaning of the curves obtained by the BCG are a true counterpart of the experiments performed on dogs to elucidate the meaning of the electrocardiogram and its abnormalities.[3]

The students of a generation ago were taught that the heart exerts its effects throughout systole, squeezing the blood out of the heart until systole is over. The BCG has taught us that the normal heart behaves quite differently. Its forces are really imparted in a burst of brief duration at the onset of systole and the last of the ejected blood leaves the heart not because it is squeezed out, but because of the energy imparted earlier that set the blood stream in motion. Once set in motion it continues to flow until resistance stops it.

This new concept suggests that there are new and important aspects of the heart function for clinicians to consider, such as the duration of the "cardiac effort" which is much less than the duration of ejection. This being the case one would expect and one actually finds that strong young hearts have a more explosive contraction which endures a shorter time than older hearts and those weakened by disease. The amplitude of ultra-low frequency records definitely diminishes as age increases and form abnormalities appear with increasing frequency as age advances, even though apparent good health is maintained.

The BCG as a measure of functional efficiency is hard hit during acute myocardial infarction, during aginal attacks. There appear incoordination of the cardiac contraction, a phenomenon not recognized in other ways by the clinician, although he can infer it.

The important thing here is the recognition that classifying cardiac disease according to etiology or anatomical lesions may or may not be accompanied by the physiological abnormalities of myocardial weakness and incoordination. Many conventional methods widely used at present may not reveal the existence of weakening of the myocardial force during contraction which are clearly brought out in the BCG.

The BCG has helped us to a new conception in clinical cardiology, that of incoordination of cardiac contraction which alters the force of the ventricular contraction and distorts the normal waves of the BCG. When the time course of the force BCG becomes irregular, we must think of asynchronism of contraction of certain muscle bundles and of the ventricles as a whole contracting irregularly.

L.H.N.

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The Role Of Platelets In Arterial Thrombosis

Atherosclerosis is almost universally present in adult Americans. The ischemic complications of atherosclerosis account for over half of all deaths in the United States. One of the important factors involved in death from atherosclerosis is arterial thrombosis. It is therefore obviously important to understand the factors involved in arterial thrombosis. Glynn, et al.[1] found out a well-recognized fact that arterial thrombosis only occurs when the endothelium is severely damaged exposing the underlying collagen. It is then that platelets come in contact with the collagen.

The initial step involved in the formation of an arterial thrombus now is adherence and aggregation of platelets to the collagen. Masses of platelets soon become interspersed with layers of fibrin and red cells. The platelet mass soon diminishes and fibrin becomes a prominent component. This emphasis on the latter phase is perhaps the reason that observers have in the past identified thrombogenesis, not with platelet aggregation but rather with coagulation.

The process is apparently a self-generating one. As the platelets in the mass swell they become degranulated and liberate both serotonin and adenosine-diphosphate (ADP) which plays an important role in the further growth of the platelet mass. In addition tissue thromboplastin is released at the point of injury and also stimulates coagulation. The central mass of the thrombus is composed of lightly packed platelets aided by released ADP. In the periphery of the thrombus, the platelets undergo structural change and become interspersed with layers of fibrin and this is what lends stability to the thrombus.

When for any reason the coagulation component is greatly suppressed, the platelet mass that forms is probably readily broken up and dispersed. It is this process which probably causes temporary retinal failure or cerebral anoxic attacks. Whether the thrombus will break up and lead to microcirculation emboli or whether extension of the thrombus will occur, clearly must depend upon factors that can either degrade ADP or neutralize thrombin.

It would appear that the initial reaction of platelets with an exposed surface of the artery has many of the characteristics of white cell response in immune injury, inflammation, and phagocytosis. Because when the platelets are exposed to such stimuli they, like the leucocytes, release factors that increase vessel permeability. This primary reaction of platelets to surfaces could be important for several reasons. Drugs with anti-inflammatory properties might influence the early stages of thrombosis. Then there is the possibility that under conditions of inflammation, platelet aggregation could itself injure the vessel wall.

After the first day the bulk of the platelets in a thrombus have disintegrated, and there is a marked increase in the amount of fibrin together with a considerable reduction in the size of the thrombus. The white cells which have also infiltrated the thrombus also disintegrate by a mechanism as yet unknown. After two weeks such a mural thrombus becomes organized. Intimal thickenings rich in smooth muscle cells and collagen develop in which only traces of fibrin and cellular debris are encountered. The result of course is an atheroma.

When there is absent or minimal fibrin component, the platelet aggregates can be readily reversed and now arises the question as to what might be the effect of such transient platelet rich thrombi or emboli on organ function. Experimental studies on the coronary circulation by infusing ADP (which causes platelet aggregation) has been shown to lead to myocardial infarction. It has also caused damage to the microcirculation in the kidney. Similarly it is known that in disseminated intravascular coagulation, pathological processes are initiated in various parts of the microcirculation by platelet rich thrombi.

In view of the primary role of platelet adherence and aggregation in arterial thrombosis, it should be possible to influence them and thereby suppress thrombosis. Clearly drugs that only suppress coagulation will be relatively ineffective in preventing the initial accumulation of platelet material on the vessel wall although they should suppress thrombus growth and stability. But then we have the problem that organ dysfunction and pathology can be caused by transient platelet aggregates. Obviously treatment with coagulation depressing drugs although perhaps helpful may not be sufficient to control all aspects of arterial thrombosis. It is clear that effective treatment against arterial thrombosis will require something that inhibits both the initial step of platelet aggregation as well as the second step of coagulation.

In theory a drug such as heparin which affects cell membranes as well as coagulation might be useful. The only trouble is that in the usual therapeutic doses heparin does not effectively suppress the platelet surface reaction as ADP induced platelet aggregation. We must now seek agents that could prevent the formation of the initial platelet mass. Phenylbutazone has been shown to affect platelets by suppressing their response to collagen.[2] Similarly it has been suggested that linolenic acid may function to reduce platelet adhesiveness.[3]

The real problem of course in treating arterial thrombosis is that after an interval of 12-24 hours, the attack on platelet adhesiveness comes too late and any success would have to be achieved by an agent that could lyse the fibrin in the clot. Phenylbutazone could be just such an agent.[4]

The important point in all this is that we are gaining an understanding of the mechanism involved in pletelet adherence and aggregation and the relationship of these to arterial thrombosis and disease. This should facilitate the development of better therapeutic techniques for the prevention and management of arterial thrombosis.

L.H.N.

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Biologic Effects Of Environmental Radiation Exposure

Little[1] points out that radiation exposure can shorten life, lead to cancer and produce greater abnormalities in the offspring from irreparable damage to the genetic material of cells that survive radiation and still retain the capacity to propagate. The effect on life expectancy was clearly demonstrated in radiologists ages 35 to 44 who were found to have a shorter life than internists in the same age group.[2]

The carcinogenic effects of ionizing radiation in man has been demonstrated for a wide variety of neoplastic diseases. They are however the result of large exposures. The leukemia incidence is known to be high in persons with whole body or large tissue exposure such as occurred in Hiroshima and Nagasaki. Radium dial painters develop osteogenic sarcoma.[3] Alpha radiation from high concentrations of radon and its daughters in the air has been found to produce a high incidence of pulmonary carcinoma in underground mine workers exposed to this gas.[4] Alpha radiation from Polonium^{210} a naturally occuring trace element in tobacco has been proposed as a carcinogenic agent in cigarette smoke.[5]

Women who underwent multiple fluoroscopic examinations during treatment of pulmonary tuberculosis by closed pneumothorax showed a high incidence of breast carcinoma.[6] Some tumors may yet appear later in people already exposed. Relative cancer risk is 40 per cent higher in children whose mothers received diagnostic X-rays for pelvimetry during pregnancy.[7] The fetus is so sensitive that even low exposures, a simple X-ray film of the abdomen of the mothers (1 rem) results in significant increase in the incidence of cancer in the child including leukemia.

Definite evidence of genetic defects in the offspring of irradiated human beings is still lacking. However, in animals like drosophila and mice it is conclusive. Russell[8] found seven specific locus mutations in several hundred thousand offspring of irradiated mice. Assuming such results can be extrapolated in man, then the total dose necessary to double the natural mutation rate in man would be of the order of 25 to 30 rem for acute radiation exposure, but probably 100 rem or more for chronic low level exposure.[1] It is easy to see that such doubling of mutation rate of the human population would eventually have serious consequences. The background rate is 4 rem per generation so that the doubling dose rate would amount to 6 to 25 times the background. If we should be subjected to a nuclear conflict, those who would survive could conceivably give rise to a generation with an intolerable number of deleterious genetic mutations.

Chromosome damage in leucocytes after radiation exposure has been described. Persons who received an exposure of 12 to 35 r during the course of a simple X-ray examination showed persistent chromosome aberration in their leucocytes.[9] This was also observed in a group of radiation workers with mean chronic life time exposures of 1.4 rem per year (about 10 times the background radiation.[10]

A final biologic effect of radiation is the production of developmental anomalies in the fetus. These may occur with exposure as low as those incurred during diagnostic X-ray examinations of the mother. Little[1] believes sensitivity is probably maximum in human embryos during the 2nd to 6th week of development. This clearly would preclude any pelvic irradiation in women of childbearing age to any period except for perhaps 10 days after menstruation.

The national committee on radiation protection has suggested maximum permissible radiation doses.[11] However from what we have seen above the idea that radiation in doses below a certain level produces no biologic damage of consequence is obviously not true. Based on theoretical considerations and on recent observation in animals and man, probably no threshold exists below which no genetic damage would occur from long term effects of radiation. In this case any additional radiation exposure above background is potentially harmful. In setting "acceptable risk" standards, the question is one of weighing possible risks from radiation exposure against the value of the diagnostic examination.

In most instances the radiation risk is small as against the risk incurred if an indicated examination is not done. Nevertheless the radiologist and the physician must always weigh the factors involved. There are of course exceptions such as children with congenital heart disease who received up to 585 r of diagnostic X-rays and follow up fluoroscopy, 95 per cent of which would have been avoided by substituting chest films instead.

Many single measures can markedly reduce exposure from external sources especially medical X-rays. This is recognized in the production of new equipment and technics by radiologists, as well as a more critical and conservative attitude towards taking X-rays and using fluoroscopy.

Safety factors for internal exposure are much more difficult. Obviously the problem of protection against internal exposure involves primarily those of avoiding ingestion or inhalation of the isotope. Our knowledge of possible sources such as radon gas in mines, living inside homes of radioactive rocks or over radioactive granite, should help us to avoid some of these hazards. Knowledge of the physical and biological properties of the damaging isotopes can also be of help as well as of the food chains whereby the isotopes are concentrated until they finally are ingested.

With short half like isotopes, contaminated food can be stored until sufficient decay has occurred. For example milk contaminated by I^{131} with a half life of eight days may be canned or converted to butter or cheese for future consumption. Absorption of an isotope may be depressed by dilution or with a stable element whose chemical properties are similar to those of the isotope. Once absorbed the isotope may be more readily excreted by the same technic. Excretion of Na^{22} or H^3 will be enhanced if large quantities of stable Na or water are ingested. With many important isotopes such as Sr^{90} and Cs^{137} once the element is deposited in the body little can be done to prevent radiation exposure.

At present 90 per cent of the excess radiation exposure to the world population above normal background comes from clinical sources primarily diagnostic X-rays. Over these we can have some control. In the future however radioactive isotopes released from bomb detonation and atomic energy installations may become a significant factor. If indulged in on a large scale civilization will become extinct. In this case mans science and technology which has brought blessings to mankind, will also become the instrument of his undoing.

L.H.N.

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The Safety Of Modern Processed Foods

There has been an expanding use of chemicals added to foods during processing for various technological reasons as well as to improve taste and add convenience to their use. There has also developed marked use of agricultural chemicals such as pesticides and plant growth regulators to increase agricultural production. It must be admitted, however, that despite the best use of agricultural practices, residues of such substances may remain in foods. But the advantages derived from food additives and the chemicals used to increase agricultural production must be weighed against possible adverse effects on health resulting from these practices.

Agene (nitrogen trichloride) is a chemical oxidizing agent used to bleach and mature wheat flour. This agent definitely produces running fits in dogs that eat such flour. Is it also damaging to humans? It turned out that 19 subjects given such flour did not develop clinically evident effects. Agene is now known to produce methionine sulphoximine in 5 per cent of the methionine in flour. This means that for man not enough methionine is destroyed to prevent its utilization in protein building. But methionine sulphoximine is toxic to humans and in sufficient dosage can be toxic. We must alert to this possibility in undernourished populations.

When the use of agene fell into disrepute, the milling industry turned to other maturing agents notably chlorine dioxide. This bleaching agent does interact with nutrients in the food to reduce the tocopherol content. It causes loss of essential fatty acids in large amounts. However there appears to be little chance of oxidative destruction of essential fatty acids in flour which is treated with amounts used commercially. It would seem therefore that its normal use does not present a hazard to humans living on a normal diet. What it would do to humans on certain abnormal diets is not known.

Ethyleneoxide has been proposed for fumigating foodstuffs or sterilizing foods for which steam sterilization is not practical. Studies with this substance on rats given stock or purified diets exposed to ethyleneoxide caused growth depression because of destruction of certain essential aminoacids. However the quantity of adverse products is too small to cause any alterations in food greater than those resulting from cooking or normal deterioration in aging and much less than that from even minor spoilage by bacteria, fungi, and insects.

Another chemical commonly used to fumigate wheat, methylbromide, can damage the histidine residue, but here also amount of reaction occuring under typical fumigation conditions was negligible. At most 1-2 per cent of the total amounts of aminoacids in food proteins are damaged and this is too small to produce any nutritional or toxicological effects. This does not rule out the possibility that certain persons may be especially sensitive to this agent and respond in an unpredictable manner.

Some solvents have been used to remove lipids or water or both in food processing. It was believed that this process was safe if the toxic solvent residues were not left in the foodstuff after processing. What was not known was that the solvents may interact with components of food to produce new compounds that could be toxic. The best known example of a solvent-food interaction is that which occurs between trichlorethylene and proteins. Thus soybean meal extracted with this solvent was toxic to cattle. They showed bleeding from body orifices and into the skin. Campbell and Morrison[1] found that fish protein treated with this solvent loses its histidine and methionine. Furthermore some solvents also form new compounds like chlorocholine which are directly toxic.

Sulphur dioxide has been used as a food preservative for centuries. In small amounts however it produces no deterious effects unless the diet is deficient in thiamine and biotin, which is destroyed by this preservative.

Nitrates or nitrites in the diet or drinking water can lead to methemoglobinemia. They also produce nutritional effects as well for they reduce vitamin A stores and also reduce thyroid activity which is needed for the liver conversion of carotene to vitamin A. This has important therapeutic implications since many patients with angina pectoris are kept on nitrates for long periods of time. The undesirable effects of these therapeutic agents could be reduced by intermittent administration.

As far as pesticides are concerned relatively little seems to be known of possible nutritional effects although both DDT and dieldrin are known to decrease liver storage of vitamin A.

EdTA, a chelating agent is useful for removing metals which impart undesirable colors for foods. Only at high levels however (1-4 per cent) were toxic effects noted in young rats due to decreased absorption of iron and increased excretion of iron in the urine. There were however no effects on calcium excretion or its levels in serum and bone.

We have thus seen that intentional or inadvertent addition of chemicals to foods during processing may exert a broad variety of nutritional effects that fall into two categories. The first involes a chemical reaction between the additive and food components which result in the formation of new compounds which may be toxic. The additive responsible for such changes may not even be present in the food after processing, but the nutritional effects are detectable by subsequent damage.

The second type of nutritional effect is that exerted by certain additives on the utilization or metabolism of nutrients after ingestion of the food. Such effects result from chlorinated pesticides and nitrites.

There is little doubt that as foods become more and more sophisticated and their production more complex, it may be expected that the use of additives, pesticides, solvents and preservatives will become more widespread. As the present trend towards processed foods continues, food technologists, nutritionists, the physician, and also the public must be aware of the interactions between food constituents which occur in food processing. Obviously there is need for an integrated approach to food safety and evolution of a program.

Testing procedures for the evaluation of the safety of modern processed foods must be highly refined and critical. They must include studies in which the food is given to animals under conditions which can reveal any nutritional relationships, for it is no longer possible simply to determine the amount and toxicity of chemical residues in food.

It should be pointed out at this point that despite the fact that food additions can exert importent nutritional effects there is no cause for undue concern about the safety and nutritional adequacy of our population consuming large amounts of processed foods. The important point is that we should be aware of the possibility of these effects and that all those concerned with food production, processing, and evaluation should realize that some of these effects can have serious consequences.

L.H.N.

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The Two Doctors – Yesterday And Tomorrow

Reuben I. Solway, M.D.

■ Some fifty years ago, Conan Doyle fashioned Sherlock Holmes out of the image of his old teacher of medicine, Dr. Joseph Bell of Edinbourgh. Of Dr. Bell he wrote:

"He would sit in his receiving room with a face like a red Indian, and diagnose people as they came in, before they even opened their mouths. He would tell them their symptoms, and even give them details of their past lives, and hardly ever would he make a mistake."

Dr. Bell was the prototype of what I chose to call the 'educated guess' school of medicine. This breed of doctors dominated the medical scene during the first half of the twentieth century; they carried on the tradition of Claude Bernard, of William Osler, of Sigmund Freud, of the multitude of enquiring physicians who have moved the study of medicine from witch-craft to science.

In general, these doctors had little information to guide them beside the data they gathered with their five senses. When I went to medical school (I graduated in 1940), the emphasis was on clinical observation, on data gathered by looking, hearing, feeling, smelling, and tasting; it was considered poor taste to wait for a laboratory or a radiological report.

The ideal physician in those days was the general practitioner, the physician who could perform miracles of diagnosis and treatment with only the materials found in any kitchen. We were trained to be self-reliant, to be able to operate effectively if we were set down in the midst of the Canadian bush.

The most dramatic moment in one of the early Dr. Kildare movies was the episode in which the hero did an emergency blood-transfusion on a busy street, using a watch-glass to cross-match, and some enema tubing to conduct the blood from donor to recipient. My greatest ambition when I entered practice was to do a delivery at home; I encountered a retained placenta and never tried again.

On looking back, I must admit that we doctors of the older generation relied heavily on the paraphernalia of witchcraft. We fostered the notion that the doctor is some sort of god-like creature who moves within a magic circle, and manipulates evil spirits disguised as illnesses; he exercises these malevolent miasmas by invocation, by foul-smelling potions, by the laying on of hands.

Characteristically, the doctor was expected to dress in a distinctive way. In early times, the medical man appeared in a costume resembling that of a buffoon. I recall in my student years that the specialists had their trademarks: the cardiologist wore a peaked collar, the surgeon a sports jacket, and the obstetrician displayed a white carnation in his lapel. A popular story that epitomizes the idea concerns the missionary who was captured by a tribe of cannibals, and tied to a stake while preparations were made to boil him in the communal pot. The dancing and the singing got wilder and wilder, the beating of the drums rose to a crescendo, and the excitement mounted to fever pitch. Suddenly everything stopped, as though on signal, and a crashing silence descended on the camp. All eyes turned to the hut nearest the prisoner. Suddenly the curtain parted, and a huge man stepped out. He was smeared from head to toe in white clay, his face was streaked with colors, his dress was of animal skins, his head-gear of the plumage of many birds, and in his hand he carried a club mounted with a human skull.

As he stood there, outlined against the dark forest, a tiny voice in the outer circle of onlookers whispered:

"That's my son, the doctor!"

Treatment in those days, too, was comparatively simple, we used aspirin, digitalis, morphine, and phenobarbital in the bulk of our prescriptions. To lend weight to the value of these concoctions we invented elaborate formulas, mixtures, and recipes, in many colors, of varied consistencies, of forbidding palatability. We wrote our prescriptions in Latin, using an antiquated system of measure, formulated in bizarre manufacture.

I can still remember a multitude of therapies that today would seem barbaric: the feeding of infants by rigid schedules, the wholesale tonsillectomy of helpless children, the spaying of menopausal women, the application of mustard plasters

An address by Reuben I. Solway, M.D., of Westport, Connecticut, practicing physician, columnist and medical writer at graduation ceremonies for the Norwalk Hospital House Staff on June 23, 1966.

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and of turpentine stupes at the least provocation, the assiduous purging and hosing of the colon. The doctor was expected to "do something"; he proved his worth by devising complicated, unpleasant treatment. The patient was always reassured when his doctor resorted to the laying on of hands. In this regard, my favorite story concerns the theater manager who stepped out during the first intermission, and gravely announced:

"Ladies and Gentlemen, your attention, please. I must announce that the leading actor has just dropped dead, and that if you line up on the way out, your money will be refunded."

A woman stood up in the balcony and cried out: "Give him an enema!"

The manager blinked and repeated his announcement.

"Your vouchers will be honored at the matinee a week from today."

Again the woman stood up and shouted:

"Give him an enema!"

The man turned to acknowledge the heckler.

"Madam, I don't know whether you heard me, but the man is dead. What good will an enema do?"

The woman cocked her head, and raised her arms to her sides.

"I don't know what good it will do," she responded, "but it can't do any harm!"

The forces that are molding the future of medicine began to take shape at the turn of the century in such remote disciplines as mathematics and physics. Bertrand Russell and a coterie of philosophers proved that mathematics is a branch of logic, thus making possible computerized and automated technology. They devised a minimal language that reduced all scientific thought to discrete symbols expressing propositions, classes, and relationships. The language has immense force and range since it clarifies the basis for inference of one proposition from another; it became the language of the computer.

The transition from theory to practical machine was accomplished by Claude E. Shannon who, while still a student at M.I.T., wrote a paper on the translation of these symbols into electrical circuits. He showed that these circuits could be analyzed and simplified by representation as statements in symbolic logic, the so-called Boolean algebra. Single ideas, then, could be represented by single symbols, and aggregates of ideas could be handled by electrical circuits to yield meaningful new ideas.

In 1956, W. Ross Ashby published a short paper on the design of an intelligence-amplifier. He noted the intellectual powers of man are distinctly limited; the individual with an I.Q. of 150 is rare, and the person with an I.Q. of 200 simply does not exist. Yet we are able to amplify other faculties; a man using a shovel to move coal can convert his 1/10 horsepower in into 1000 horsepower in a steam-engine. Why, then, can we not devise a machine to amplify intelligence so that we would be able to expose our problems to an I.Q. of 1,000,000?

Ashby's proposal was quite simple. Since ideas may be represented by symbols, we set our machine to work turning out a host of random ideas much in the fashion of a child doodling on paper. From this multitude of ideas we select a group which are relevant to our problem, and discard those which have no bearing. Much like the gardener who strains his dirt by throwing it against a sieve, we refine the possible alternatives until we come closer and closer to the required solution.

The principle that Ashby's machine illustrates has been with us for thousands of years. Whenever man invents a device to help him with his work, he raises himself to another level of existence. When he went from stone tablets to the printed page, he could stop scrounging for food, and could sit around and think. Much as we hate to admit it, thought requires leisure and leisure requires material abundance. More than that, we have to admit that philosophy is attendant on technology, and not the other way around.

Medicine is entering the Age of Automation, and this encounter forces us to take another, sober, look at the way we think. A great deal of time in the old days was consumed with doing menial tasks. Not too long ago, we did urinary sugars by boiling Benedict's solution with a few drops of urine, and waiting for the yellow color to appear; we went through similar complicated procedures for protein and for other constituents of the urine. The process of urinalysis has been simplified; we merely dip a treated slip of paper in the urine, and read the results against a scale. The range of tests we can ask for, and the information we can so gather is tremendous; like Ashby's intelligence-amplifier, we have at our disposal a great deal of information, some of it negative information, from which we can sift those results we deem pertinent. The process of making a diagnosis is no longer based on the 'educated guess'. on shrewd inference, but is generated by the observation of information ground out by machines that do not suffer from fatigue. While I am in an 'admitting' mood, I might as well admit that we are practicing better medicine. Scientific method has invaded medicine, and is succeeding in driving out the remnants of mysticism that have remained with us since the days of witchcraft.

I envy the young doctor who is enbarking on his new career after completing his hospital training; he faces a most exciting and challenging future. I predict that he will be a more harried person than we were, for the demands on him will be much greater, and he will have to display the versatility of da Vinci, and the dedication of Paracelsus. He will have to know a good deal about sociology, about politics, and about the behavioral sciences. He will have to be a strategist with an array of powerful tools at his command.

I predict that the ten years just past, and the ten years to come will mark a true revolution in the philosophy of medicine. The advances we shall make shall equal in scope all the advances made in the past two thousand years of ministering to the ills of mankind.

Some ten years ago, I audited some courses in mathematics and in the philosophy of science. In a naive way, I tried to apply what I had learned to some of the problems I encountered in practice. Uppermost in my mind is a woman who was referred to me by a psychiatrist for management of her drug consumption. The woman was a brambled heap of emotional problems mixed with drug addiction, and with plain, garden-variety alcoholism. After months of counselling she began to show some improvement. One day, as she left my consultation room, her husband confronted me and pumped my hand.

"Thank you, Dr. Solway," he exclaimed, "for the help you gave my wife. I'm so glad we stopped going to doctors, and came to you."

"But I am a doctor," I protested.

"Oh, no!" he replied, "you are a mathematician!"

I wish I were worthy of the compliment.

I am certain that the new doctor will be humble. His humility will spring from the intuition that nothing really replaces experience when dealing with the human animal. All the fine machines, all the exhaustive tests are of little value unless the doctor remains a creative, reasoning, director of operations; otherwise, we are left with a lot of shiny equipment operated by an 'educated dope'. If the doctor does, however, retain those qualities that are the heritage of William Osler, and of John Hunter, what a doctor he will be!

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Background Of The Litchfield County Medical Association Of 1767

Gert M. K. Wallach, M.D.

■ Every American who is interested in health, and that means everybody, should commemorate that cold winter day in January 1767 when thirty-one physicians—who rode their horses as much as fifty miles in each direction—assembled at the old Court House in Litchfield to found the Litchfield County Medical Association.[1]

It was the beginning of one of the most forward looking and persevering efforts to lift Medicine out of its dismal inadequacy and to start that glorious development which has raised American healing arts to their preeminent position of today and certainly has not yet ended.

Let us not forget: in 1767 there existed in this country one Medical School only—that of the University of Pennsylvania—and this school had not yet graduated anyone who had finished its full course of instruction. Medical education ranged all the way from no education at all to varying years of apprenticeship. Extremely few American physicians had studied abroad and none from Litchfield County.[2]

Except in New York City,[3] there was no licensing system. Everyone could call himself a physician and hang out his shingle.

There was no protection for the patient, by law or otherwise, and there were no established principles of Ethics, or anyone who could enforce them.[4]

There was no medical journal; the first one in this country was founded twenty-nine years after the beginning of the Litchfield County Medical Association, and the son of one of the founders of our Society was one of the three editors who started this venture in 1796.[5]

There was no post-graduate education. Problems, worries, observations, findings of the different practitioners, could be communicated only by word-of-mouth, as medical pamphlets were printed very rarely. In Connecticut the first medical book was not written until 1811 (in Goshen, Litchfield County).[6]

Obviously, a society was needed which could examine and license competent fledging physicians; which could and would enforce standards of Ethics among physicians and between doctors and suffering patients; which could provide a meeting place where medical men could exchange their findings and opinions and where their knowledge would be enlarged. And, in the future these societies would be instrumental in founding medical schools and promoting developments we know today.

But why did this most successful and enduring effort start in the hills of Litchfield County, Connecticut? After all, this is not a region which through the Atlantic Ocean is directly connected with the ancient seats of learning in Europe; this is not a section which contains large and navigable rivers which tie it easily to the cultural centers of the East. As a matter of fact, Litchfield County was the last Connecticut county which was settled,[7] and in 1767, when those thirty-one physicians first met, it had not been settled completely. The northern regions of the county—around Norfolk, Colebrook, Winsted, Hartland, Barkhamstead[8]—were just cut out of the primeval forest. It was a typical frontier section like the American West of the nineteenth century. Though not yet fully developed, many of the county's inhabitants, in typical frontier fashion, thought the region already overcrowded and left again—mainly for Vermont which had just been opened up; and Litchfield County gave to the Green Mountain State practically its whole early leadership (for instance: Ethan and Ira Allen; Thomas Chittenden, the first governor: Seth Warner from Roxbury, and Remember Baker from the same town).[9] It is obvious that the foundation of the first County Medical Association in Litchfield County, in this then backwoods region, is a kind of miracle.

It is more understandable why the Association was founded at that particular time. 1767 was in the period between the end of the French and Indian War and the beginning of the Revolutionary War. Many of the founders of the Association had been prominent physicians of the Connecticut regiments that served in the war which ended the rule of France in Canada and with it the constant threat to New England.[10] Timothy Collins of Litchfield had been the first minister of the Litchfield Church for thirty years and was at the same time the first physician of this community, an occurrence not unusual in New England before 1750. In 1751 he had been the founder of the Litchfield County Ministerial Consociation and resigned from his

Address given at the Bicentennial of the Litchfield County Medical Association at the Hotchkiss School, Lakeville, Connecticut, on June 20th, 1966.

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clerical position shortly thereafter. He remained, however, in Litchfield as a physician until he died in 1776.[11] During the French and Indian War he was the commanding surgeon of the first Connecticut regiment in 1755-56, and later he was in charge of the hospital of the second Connecticut regiment in 1762.[10] When in 1756 he resigned because of illness he suggested that Dr. Elisha Lord, his assistant who later settled in Norwich, should fill his place. This Dr. Lord was instrumental in drawing up the petition of the eleven Norwich physicians of 1763. More interesting to Litchfield County is the fact that Timothy Collins wrote to the General Assembly that at that time Dr. Lord performed his duty "with the Assistance of his apprentice William Abernathee who went into the army in the Capacity of a private Sentinel."[12] This Dr. William Abernathee of Harwinton is another of the founders of the Litchfield County Medical Association. Later on he had the reputation of having so many apprentices that some thought that he ran a medical school. Early physicians of the Cleveland, Ohio region and of upper New York were his students.[13]

During the French and Indian War New England physicians came in contact with British physicians and somewhat with French ones. In Parkman's "Montcalm and Wolfe" it can be read that the colonial physician was quite backward and did not believe in sanitation,[14] which practice had been introduced into the British Army in 1752 through the efforts of Sir John Pringle.[15] This must have had its effect on Dr. Timothy Collins, on Dr. William Abernathee and their colleagues.

Still, there were other frontier counties who sent their physicians to serve in the French and Indian Wars and these other counties did not found medical associations. There must have been another factor to explain the miracle of the founding of the Litchfield County Medical Association. It seems that this factor was the caliber of the men who started the venture on that cold winter night in January 1767. These men were not only physicians, they were at the same time busy in other professions and occupations. Beside ministers and farmers they were also lawyers (including the Chief Justice of the County for 17 years),[16] industrialists, high officers of the militia, enterprising merchants, members of the Legislature. In short, these physicians were public minded, they were the best the county could offer.

Their offspring proved that they were outstanding. One became a poet and the first compiler of the first Anthology of American verse.[17] Another was the chairman of the Foreign Relations Committee of the House of Representatives in Washington just before the War of 1812. He enlisted as a private in the army when his politics helped to unleash the outbreak of this war.[18] Another founder was the father-in-law and teacher of the first Doctor Welch of Norfolk, whose grandson was Dr. William Welch, one of the Great Three of Johns Hopkins University and the man who introduced laboratory methods into American medicine.[19]

These men acted on their own initiative; they acted against a hostile Legislature and population. Today it is widely believed that physicians have to be coerced by government to do the best for the good of mankind. The struggle of the men of 1767 proves that this is not true. These physicians took the leadership where it was necessary, and persuaded the public after a long and hard struggle which steps had to be taken and what was best for their health.

The spirit of 1767, like the spirit of 1776, proves that men will eventually do the best for the common good if left to their own designs.

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Recurrent Paroxysmal Atrial Fibrillation

(Twice Converted To Sinus Rhythm By Electrical Countershock)

Daniel Kahn, M.D.

■ Electrical conversion of resistant cardiac arrhythmias by current applied externally to the chest wall has proved to be safe and effective. The object is to extinguish the ectopic focus by depolarizing the entire heart, and abolishing the re-entry pathway which the ectopic front wave of depolarization traverses[1]. The sinus node then resumes its function as the pacemaker.

Prior to this electrical method, reversion was accomplished solely with drugs. Disadvantages include delay of action, potentially dangerous side effects such as quinidine and procaine amide decreasing peripheral resistance, cardiac excitability and contractility and prolonging intraventricular and atrioventricular conduction. Occasional serious toxic reactions of digitalis are well known. Furthermore, an ectopic arrhythmia may be refractory to drugs. A method which was more predictable, quicker, and safer without depression of pacemakers was sought.

Beck[2] performed the first successful defibrillation of the human heart in 1947, by applying an alternating current (AC) directly to the heart surface. Zoll et al[3] succeeded in terminating ventricular fibrillation with closed-chest AC discharge. Zoll and Linenthal and others[4,5] in 1962 included atrial tachycardias in their AC shock treatment program. Zoll emphasized, however, that the hazards of this method included possible induced ventricular fibrillation or standstill. Lown[1] pointed out that another hazard was induction of myocardial infarction in animals.

King[6] in 1934 had first shown that the vulnerable period for the ventricle is during late systole, coinciding with the T wave of the electrocardiogram. This led Lown et al[7] to employ and introduce the technique of synchronized direct current (DC) countershock. This permits discharge to be triggered by the R wave of the electrocardiogram, falling outside the T wave (20 milliseconds after the R peak) and thereby avoiding induction of ventricular fibrillation. This method has now been widely accepted as the treatment of choice in life-threatening atrial[8] as well as ventricular arrhythmias, particularly those resistant to drugs.

A case of paroxysmal atrial fibrillation, drug-resistant, with congestive heart failure, twice treated with DC shock is reported as the first patient to receive this type of treatment at the Meriden Hospital.

Report Of A Case

The patient, a 69-year-old white male, was admitted to Meriden Hospital on Nov 21, 1965, with unremitting cough of two weeks' duration, culminating in dyspnea and rapid, irregular palpitations of three days' duration. He had been treated for hypertensive cardiovascular disease for several years, with maintenance digitoxin 0.2 mg daily, quinidine 0.2 gm tid, a thiazide preparation and reserpine 0.25 mg daily. Approximately one year previously he had an episode of paroxysmal supraventricular tachycardia which had reverted to sinus rhythm with quinidine.

Physical examination on admission: Blood pressure 140/110 mm Hg, pulse 180 and grossly irregular. Patient was apprehensive with cyanosis of the lips and distended neck veins. There were rales at both lung bases; the heart was enlarged with left border of cardiac dullness percussed 13 cm lateral to the midsternal line. No murmurs were heard. There was no palpable hepatosplenomegaly or peripheral edema.

Glucose was 84 mg/100 ml, blood urea nitrogen 12 mg/100 ml, potassium 3.6 mEq/liter, SGO-T 6, LDH transaminase 90 U. T3 test was 34 per cent, PBI 3.8 gamma per cent. Hemoglobin was 12.5 gm per cent, WBC 14,100. Urinalysis was normal.

On admission chest film revealed cardiac enlargement with pulmonary edema and bilateral pleural effusion. Subsequent chest film on Nov 26, 1965, showed marked improvement with minimal cardiac enlargement and clearing of the pulmonary edema and effusions.

Electrocardiograms: The initial tracing revealed paroxysmal atrial fibrillation with ventricular rate of 190. Occasional premature ventricular contractions were seen. There was ischemic ST depression but no changes of myocardial infarction.

Hospital Course: Treatment was instituted with tent oxygen, sedation, mercurial diuretics, morphine, low sodium diet, and maintenance doses of digitoxin 0.2 mg daily and quinidine 0.4 gm every four hours were continued. Later that evening, apical rate was 160 and irregular; diuresis had begun and he had less dyspnea and cough. It was felt that this was not a digitalis-induced arrhythmia since (1) he had had it, or similar arrhythmia, at least once in the past, (2) during recent office visits his pulse rate had ranged from 88 to 96,

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and (3) he had admitted skipping digitoxin once or twice weekly.

Therefore, it was decided to continue the quinidine 0.4 gm every six hours and digitoxin 0.2 mg daily. It was planned that, if the arrhythmia persisted, digitalis would be omitted for 24 to 48 hours in anticipation of the possible need for electrical conversion.

On the second day, the apical ventricular rate was 160. Basilar rales persisted despite improvement in dyspnea and cough. Quinidine was continued in this above dose, and after anesthesia with intravenous pentothal, DC cardioversion was performed (Fig I) at 12:26 PM with discharge of 100 watt seconds. After a few initial nodal beats, normal sinus rhythm appeared. The electrocardiogram just prior to the shock had revealed short runs of ventricular tahycardia alternating with atrial fibrillation. A brief period of relative hypotension (blood pressure 90/70 mm Hg) was terminated with intravenous metaraminol. That evening, the cardiac rate remained at 76 and regular, and quinidine was reinstituted on Nov 23, 1965. On the next morning, however, the ventricular rate was again 160 and irregular, with atrial fibrillation revealed on the electrocardiogram. A trial of intravenous cedilanid 0.4 mg with constant electrocardiographic monitoring showed no significant change in pulse rate. It was considered best to withhold further digitalis in view of this lack of response. Quinidine was again started in dose of 0.2 gm every six hours and on Nov 24, 1965, electrical DC cardioversion was performed (Fig II) with 75 watt-second dosage. There was prompt reversion to normal sinus rhythm with rate of 76, from preshock ventricular response rate of 180. No fall in blood pressure was encountered. Maintenance dose of quinidine 0.3 gm every six hours was begun. Ninety minutes later, the apical rate was 180. Quinidine was continued in larger dose, 0.4 gm every six hours, and rhythm reverted to normal sinus, rate 80, within three hours without further electrical countershock. This dose of quinidine pro-

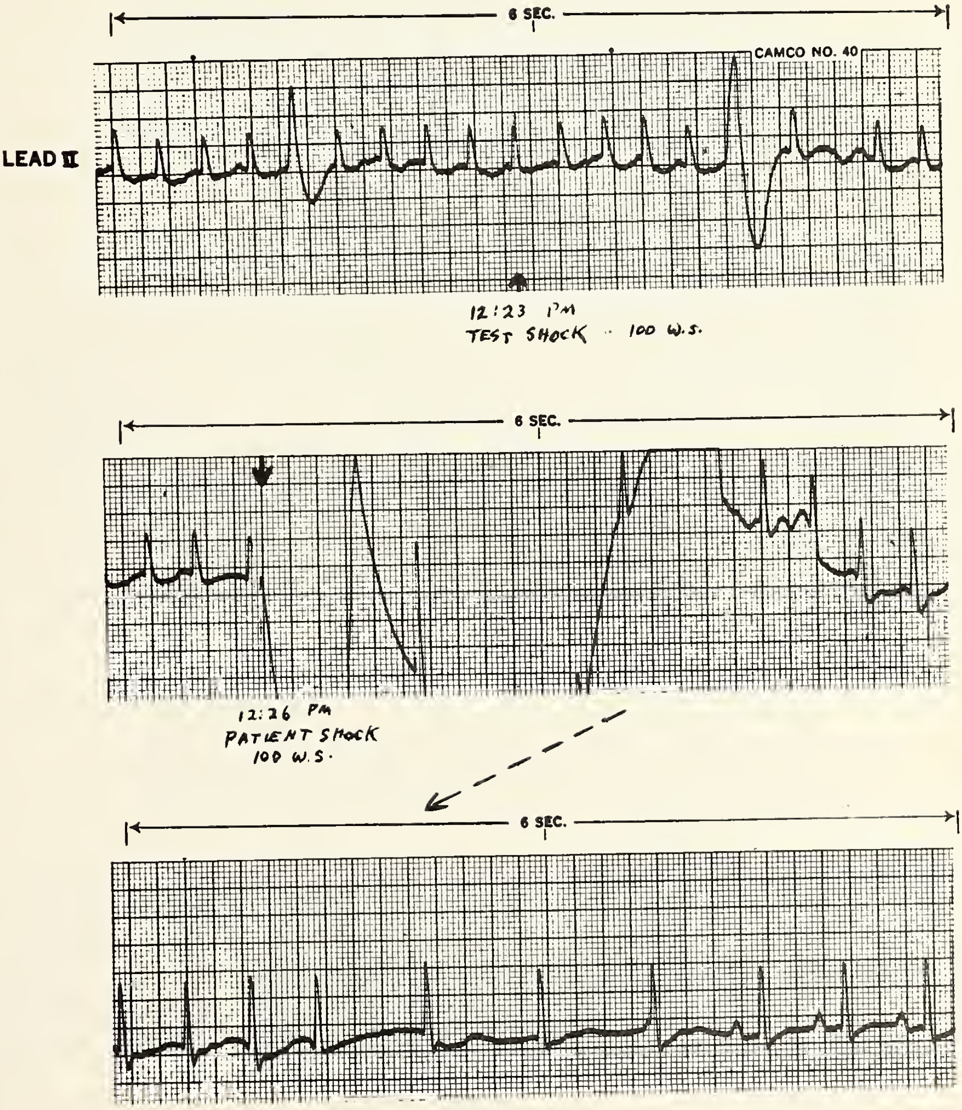

Figure I
Electrocardiogram on Nov. 22, 1965, illustrating reversion from paroxysmal atrial fibrillation with premature ventricular ectopic beats, to normal sinus rhythm. Note nodal premature and escape beats prior to resumption of sinus rhythm immediately after electrical shock.

duced slightly prolonged QT interval but no QRS interval widening. No diarrhea, tinnitus or nausea was noted. From that date to discharge on Dec 5, 1965, blood pressure and pulse remained at stable levels of 130/80 mm Hg and 80. Oral redigitalization was started on Nov 29, 1965. At the time of discharge, he was maintained on digitoxin 0.2 mg daily and quinidine 0.4 gm every six hours, as well as reserpine 0.25 mg nightly and butabarbital 15 mg twice daily. To this time, approximately seven months later, he has had no alteration from normal sinus rhythm and no signs of quinidine toxicity or of congestive heart failure.

Comment

Indications for elective reversion of atrial arrhythmias depend on the given clinical situation and the particular arrhythmia. Supraventricular and nodal tachycardia can usually be controlled by vagal maneuvers or drugs. In contrast, atrial flutter frequently requires large, often toxic doses of digitalis to slow the ventricular rate, but can easily be converted to sinus rhythm by electrical countershock.

Elective cardioversion has been most commonly used in the treatment of atrial fibrillation. Lown[9] reports 90 per cent incidence of immediate reversion to normal sinus rhythm. However, a 50 per cent failure rate in maintenance[10] has stimulated a careful determination of the indications for countershock in this arrhythmia. In the group with hyper-

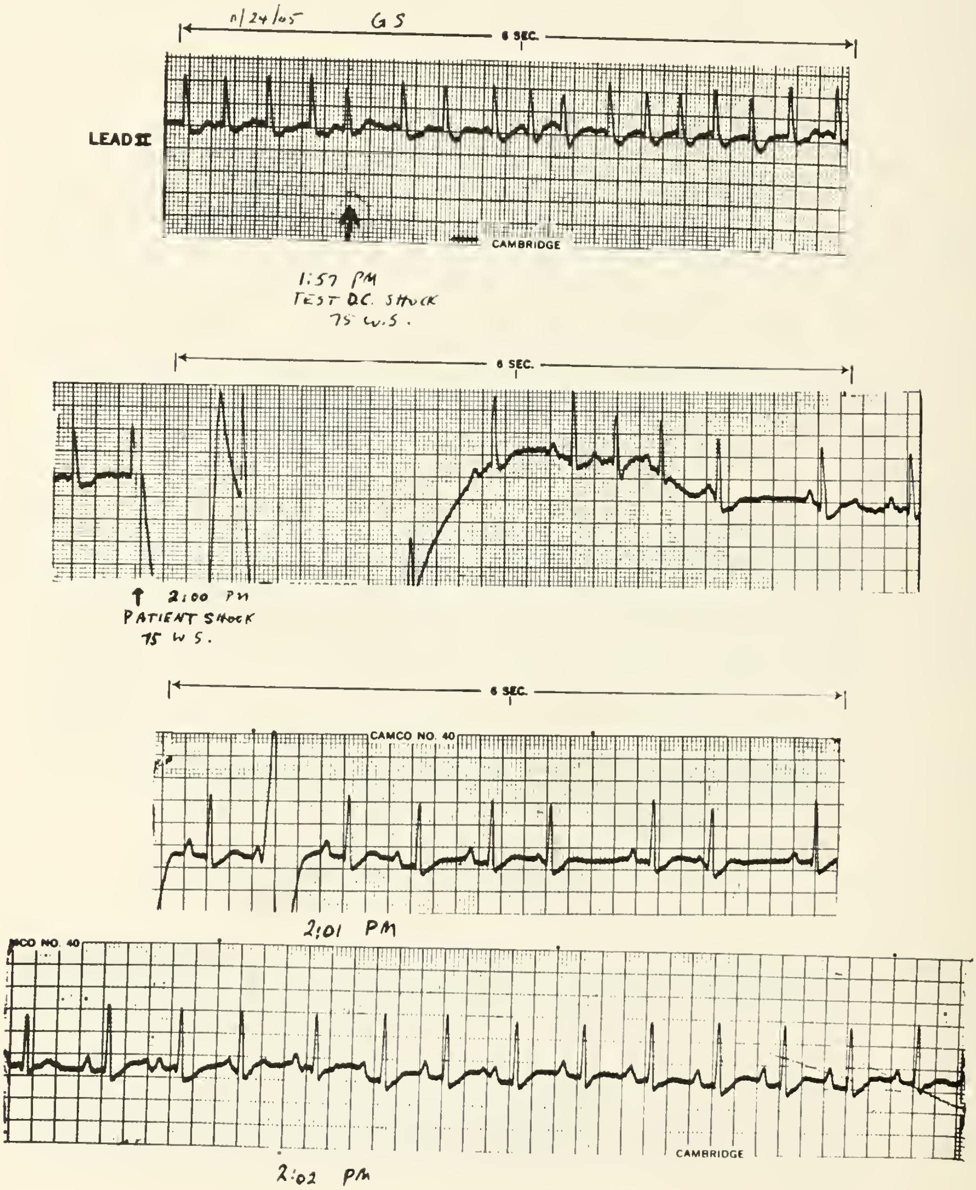

Figure II

Electrocardiogram on Nov. 24, 1965, illustrating electrical cardioversion from paroxysmal atrial fibrillation to normal sinus rhythm. Note the many premature supraventricular ectopic beats and one ventricular ectopic beat after electrical shock.

tensive or arteriosclerotic heart disease as the etiology, reasonable cardiac compensation can usually be maintained by use of digitalis and diuretics without return to sinus rhythm. This group does not display the same incidence of embolization as is seen with rheumatic mitral valvular disease. Therefore, unless refractory congestive failure is present, electrical reversion is not employed in this group.

The present case would seem to satisfy all the indications generally agreed upon in selection for electrical reversion of atrial fibrillation. First, this patient had already been on a usually adequate maintenance dose of digitalis. As outlined in the case report, it was not thought likely that the atrial fibrillation had been induced by this drug, but the possibility did exist. Morris et al[11] emphasize that during treatment of supraventricular arrhythmia, when difficulty arises in determining if the patient is under- or overdigitalized, cardioversion can be used, and the error of further intoxicating an already overdigitalized patient can be avoided. Secondly, the patient was in congestive failure which was refractory to the usual measures of diuresis, digitalis, oxygen administration, sedation and salt restriction. Hyperthyroidism had been excluded as an etiology. Quinidine, although tolerated without side effects, had not proven effective in reverting this episode. Third, the ventricular rate did not respond to digitalis, and since the rapid rate was contributing to cardiac decompensation, cardioversion appeared indicated.

Once the decision had been made to employ electrical countershock, it became essential to stop the digitalis, for it has become apparent that digitalis toxicity may be a cause of some of the serious ventricular arrhythmias occuring after electrical shock.[12,13,14] The practice of discontinuing all cardiac glycosides for at least two days before elective reversion has been advocated.[12] In this present case, the digitalis-free period was shortened because of the urgent need for reversion.

Quinidine was withheld following the first electrical reversion. A relatively large dosage had been received pre-shock in an effort to revert the arrhythmia. This withholding of quinidine may have been responsible for the recurrence of atrial fibrillation on the next day. Jensen et al[15] state that patients whose arrhythmias have previously reverted to normal sinus rhythm with either drug or electrical therapy, and have then relapsed to atrial fibrillation despite adequate maintenance drugs are very unlikely to maintain normal sinus rhythm if again reverted. Because it was realized that there may have been inadequate quinidine maintenance, it was decided to electrically countershock again, after a course of short-acting digitalis intravenously had afforded no slowing of ventricular rate.

How many times can one electrically countershock one patient? Zoll et al[16] showed that repeated countershocks were generally tolerated well, and reported one patient who had received more than 300 countershocks over a two-month period without ill effects. Thus, in the present case, the DC countershock would have been used again if it proved necessary.

A word about anticoagulants seems in order. Duchelle[17] points out that there is an added risk of embolization at the time of conversion in a patient who has recently been in congestive heart failure or fibrillating with rapid ventricular response. Goldman,[18] however, in an extensive review in 1960 concluded that the chance of embolism within 48 hours after treatment was only in the order of 1.5 per cent (as opposed to 30 per cent risk in untreated cases of atrial fibrillation). Prinzmetal[19] stated that although the incidence of embolism is not as great in this arrhythmia as was formerly believed, embolism does occur frequently when the cardiac rhythm becomes normal after prolonged fibrillation. There is no clear-cut unanimity of opinion regarding which patient should receive anticoagulants, except in the patient who has previously had a thrombo-embolic episode. The present patient did not receive anticoagulants because of the absence of previous thromboembolic occurrences, the short duration of the arrhythmia, and the urgency of the situation, which did not allow time to effect a therapeutic level with the coumarin class of drug.

The actual technique of cardioversion has been extensively reviewed.[20] It has proven to be safe, rapid and well tolerated. The period of general anesthesia need not be prolonged; the objective is to induce transient amnesia rather than complete unconsciousness. Recently, Stock[21] has described the use of this method without anesthesia, although the possible need for repeated shocks might alone justify use of anesthesia, since the shock may be considered a frightening experience by the patient.[22]

Summary

A case of paroxysmal atrial fibrillation with rapid ventricular response refractory to drugs, and in congestive failure, was treated with electrical countershock twice within two days. The feasibility of this form of treatment at the community hospital level is illustrated by its relative ease and safety.

The indications for this procedure, and concomitant drug treatment have been reviewed.

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The precise and intelligent recognition and appreciation of minor differences is the real essential factor in all successful medical diagnosis—Eyes and ears which can see and hear, memory to record at once, and recall at pleasure the impressions of the senses, and an imagination capable of weaving a theory or piecing together a broken chain or unravelling a tangled clue, such are the implements of his trade to a successful diagnostician.—D. Joseph Bell, 1887, in a *Study in Scarlet.*

Adverse Emotional Reactions To Disfigurative Surgery: Detection And Management

Patrick B. Friel, M. D., Glen C. Nicolay, Ph.D. and Ludwig M. Frank, M.D.

■ This paper will consider the various psychological reactions a patient may experience when faced with disfigurative surgery and will suggest steps which the surgeon might follow in recognizing and forestalling severe psychic disruptions. Psychopathological sequelae to surgery such as postoperative psychoses resulting from reactions to drugs and toxic substances have long been recognized and attempts have been made to anticipate and explain them.[1] However, this study will deal with emotional complications associated with disfigurative surgery, focusing on breast surgery in particular.

Because the physician is so often engrossed with the technical aspects of his surgical procedures, he may unwittingly become insensitive to the anxiety and apprehension aroused in the patient scheduled for surgery. Fears and uncertainties in varying degrees can be expected almost universally in surgical candidates; however, there will be some individuals with unusual personality makeup, developmental experiences, or emotional backgrounds who will manifest distorted reactions when threatened by surgery. Such intense psychological responses are determined both by the severity of the surgical procedure and the body parts involved, as well as the particular emotional significance of the operation to the patient.

In the course of growing up, each individual gradually becomes aware of himself as a separate and distinct person. This concept of oneself, also known as one's body image, was developed by Schilder[2] who sought to demonstrate that one eventually becomes aware of a self-image which is a composite of one's physical experiences and emotional needs. This determines not only how one sees oneself, but how, in turn, one sees other people and the world around him.

The term self-concept refers to the way the person regards himself; it is an amalgam of *his* ideas, attitudes, feelings, images, etc., about himself. It is of the utmost importance to note that this self-concept is subjectively structured by the individual and, thus, is not constrained by the laws of logic or objective reality. Cameron [3] noted that the image each person has of his own body is not normally a "true" or objective representation of his body. For example, it is not uncommon for a pretty woman to consider herself ugly . . . for a small man to consider himself larger than he actually is. In the same way, we often see a man eminently successful, overtly envied and imitated by his colleagues, clearly superior in background and achievement whose concept of self is grossly at odds with all this. He may think of himself as inept, failing and inadequate to the demands levied upon him, thus acquiring his success and affluence simply by luck or chance.

Such contradictions between objective truth and individual self-concept are developed by the interaction of intellectual effort, the unique interpretation of personal experiences, and the personal evaluation of cultural and sociological forces.

Consider the varied reactions which occur when the body image is disfigured, damaged or mutilated. For example, what personal meanings might a scar have for certain individuals? What interpretations might be attached to it? Who will react to it rationally and who irrationally? Everyone, of course, will react emotionally. Let us cite a few examples to demonstrate the meanings a scar has for diverse personalities. A slash on the cheek acquired by a German Junker in a duel with sabers is displayed with pride since it connotes daring and courage. The same mark to a young lady could be catastrophic, so hated as to cause her withdrawal from society. Similarly, the loss of a finger to a laborer would engender a set of emotions completely different from those felt by a concert pianist suffering from the same loss.

There are other instances in which the reaction to physical disfiguration is highly individualized and devoid of the more or less rational bases of the foregoing examples. Fenichel[4] recognized how anxiety and self-interest can become so acutely focused in an illness that emotional withdrawal and irraitonal reactions occur. Such inward concentration is

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manifested by highly egocentric and narcissistic behavior.

Be the feeling rational or irrational, how does a woman react to the surgical removal of her breast? What are the implications bound up in her responses? What complex mental factors are involved?

Consider first the breast as a vital part of her self-image in her role as a maiden, mother and woman. Fashion has so stressed the importance of the well-developed figure, particularly the chest, that every means to show it has been exploited—pinup pictures, decollete necklines, adulation of Hollywood sex symbols, etc. It would seem that our culture has made such a fetish of the female bosom, so equated it with femininity, that a woman would be "unfemale," only "half-woman," if anything were to destroy or harm this area of her body image. Psychic distress must be expected when she is faced with the loss or disfiguration of this body part. Kolb, Frank, and Watson[5] described the frightening thoughts and questions which beset patients who face the loss of a vital part of their body image through amputation. Such anxieties are very prevalent in the case of breast surgery. Feelings and fears experienced at the earliest developmental levels recur and the patient is overwhelmed by questions so frightening that she dares not admit them even to herself, to say nothing of discussing them with the surgeon. What will happen to this part of HER when it has been removed? How will it be treated? Will the operating team revile it by making crude jokes about it? Once removed, will it be carelessly tossed into a garbage can? How is it finally disposed of? What will she be like post-surgically? Will her loss be discernible to everyone she meets? Will the world see her as a half-woman? Will she still be a sex object to her husband or will he be repulsed and revolted by her maimed body? Other morbid wonderings may force themselves upon the woman who thus finds herself threatened with breast surgery.

The writers recently had occasion to work psychotherapeutically with two women suffering relatively acute emotional disturbances precipitated by radical mastectomy. Since these two patients typify many of the points made earlier in this paper, the cases are included here in some detail.

A. L., a 39-year-old white married female, had a right radical mastectomy in December, 1961, three years before coming to the clinic. A tentative diagnosis of cancer was made before surgery and the patient anticipated total removal of the organ. Shortly after surgery, she began to feel depressed and this depression deepened over a three-year interval to moderately severe clinical depression with suicidal ruminations and impulses. Feelings of jealousy became pronounced and, ultimately, progressed to the point of overt, paranoid, delusional preoccupation. She accused her husband of making advances to other women. These accusations caused such embarrassment for the family that all social activities had to be curtailed. Trips to the beach, cocktail parties, and T.V. commercials where female models were used became the focus of her jealousies and resulted in violent tirades.

In reviewing her developmental background, the dynamic factors that contributed to this pathological, emotional reaction to surgery are evident. She described her mother as a domineering, demanding, hypercritical, bossy, and emotionally cold woman. The father was pictured as a passive, weak individual who submitted without a murmur to this domination by his wife. This gross transposition of roles—the mother acting as the head of the household, the father as the submissive partner—created conflict in the mind of this patient in terms of what a woman's role and, ultimately, her own role should be. She realized early in her life that mother was the significant parent, the one she had to try to please. Mother de-emphasized femininity both in attitude and in her actions. The patient was dressed in "old-fashioned straight dresses" that were not calculated to do justice to her developing figure. Academic success was the only way for the patient to gain a measure of acceptance from mother and this she pushed to the ultimate. Despite an I.Q. only slightly better than average, she managed to gain the honor roll all through grade and high schools. She then worked her way through college, earning a B.A. degree. After college, she held a number of important, responsible, executive-type secretarial positions and in these she excelled. Her need to please and excel won the admiration and gratitude of her employers who had now come to replace her mother in terms of importance.

She married at 23 but found herself uncomfortable in the role of wife. She felt inadequate and unsure of herself. She was plagued with feelings of jealousy. These difficulties were accentuated when the husband paid attention to another woman at a cocktail party, two years after their marriage. The premature delivery of a seven-month stillborn, one year later, raised more doubts. She gave birth to one child, a girl, but her inability to conceive again and satisfy her husband's desire for more children threatened still further the concept of her adequacy as a wife, a woman, and a mother.

This patient's characteristic approach to life was based on the premise that acceptance was predicated upon performance. As a child, she gained a measure of recognition and avoided excessive criticism from mother through scholastic achievement. This same mechanism served her adequately in her position as a secretary where performance was rewarded with approval. Marriage presented a challenge. Femininity was downgraded and de-emphasized by virtue of childhood experience. The application of her basic formula for approval demanded that she excel as a female if she were to succeed as a wife. She felt poorly equipped to meet this task. Her doubts were accentuated by her husband's wandering attentions and by her inability to provide him with all the children he wanted. It becomes clear in this context why the removal of her breast constituted such a threat and caused this lady to recompensate into a depressive, paranoid psychosis.

M. C., a 31-year-old white female, sought help because of depression with suicidal impulses, preoccupation with her physical well-being, cancer phobia, and recurring attacks of severe anxiety, with the usual physiological concomitants of tachycardia, tachypnoea, hyperventilation, hyperhidrosis, and insomnia. These symptoms began 10 months earlier, following a right radical mastectomy for cancer. Prior to surgery, the patient did not think that the lump in her breast was cancerous; she preferred to deny this possibility, a denial which was supported by the conflicting medical opinions she had received. She ultimately agreed to have a biopsy. After waking from the anesthetic, she had what she describes as an intuition, but what really amounted to a realization that the whole breast had been removed. She felt very angry; she felt cheated. In her words, "I had two and they stole one." She refused to talk to her surgeon for three days after surgery. When he came into the room, she would turn her back on him, would have nothing to do with him, and felt it would have been much kinder if he had allowed her to die with cancer. Both of this patient's parents were alcoholic and though the mother was the dominant partner the patient felt closer to the father and tended to identify with him. She related with much feeling how she would go to bars and taverns and drag her mother home, how she resented her mother's amorous advances to various male companions. The patient was made to assume more than her share of responsibility in the home. She envied her brother because of the freedom he enjoyed. She had a poor school record; her grades were in the D and E range. She had trouble with her teachers and truancy and delinquency also punctuated her school record.

At home she felt her parents hated each other. She felt unwanted and unaccepted by both. In high school she felt left out and her pathological behavior was a way of demanding attention at a price. After graduation she had a neurotic work record for five years, changing from job to job. She then entered the Air Force, made a marginal adjustment, and received an honorable discharge two years later. For the past five years she has worked in a factory job, apart from some absenteeism, has had no other major adjustment problem.

This patient grew up in a cold, rejecting environment. Her natural desire to feel wanted, loved, and accepted was never satisfied. As a result, she yearned to have that legitimate desire fulfilled. She contemplated marriage as a method of obtaining her goal. In fact, three times she broke off relationships with men when these had progressed to the point of engagements to be married. This behavior was both a reflection of her desire to be accepted as well as of her fears that she could never be loved. A marital relationship would demand living out the feminine role, a role never attractive to her. Her mother's behavior had made it uninviting. Actually, she felt closer to her father and tended to imitate him since his lot seemed less objectionable than mother's. Her envied brother "had it made" with no responsibility. Thus, men were envied, but they offered her some hope of gaining the love and acceptance she so wanted and needed. Nature seemed to make that task more difficult for this patient because she is tall, thin, and ungainly. To her, removal of her breast was, in effect, the removal of her only meager hope of acceptance. To her, death from cancer was more acceptable than the actual rejection she now felt would be her final lot in life.

It is clear that any woman who faces the threat of mastectomy has major adjustments to make. Each such woman faces the risks that are involved in any form of major surgery. For many in whom malignancy is identified, the operation connotes the pronouncement of a death sentence despite the frequently favorable prognosis. For all, there is a major alteration of the self-image and the myriad consequences of this. Should the surgeon, therefore, expect serious psychiatric aftereffects in all such patients? Experience indicates that such is not the case. Many women undergo this operation, experience the anxiety inevitably accompanying it, occasionally exhibit some short-lived depression, but then move on to resolve the anxiety and successfully adapt to what has occurred. This might be described as the expected or "normal" reaction. On the other hand, as these two cases indicate, some women are overwhelmed by the surgery and its meaning to them, and find it impossible to make the necessary "normal" adjustments. Instead, they feel devastated by what has happened to them. They have lost a previously satisfactory personality integration and are now incapable of accepting themselves as they are. Thus they develop a neurosis or a psychosis.

It is the authors' opinion that the surgeon can predict which of these two reactions—normal or pathological—his patient will exhibit postoperatively, and that he can assist the patient in making the necessary adjustments to prevent a significant pathological reaction. The following suggestions are offered to serve this dual purpose. Their aim is to help the surgeon to relieve much of the patient's anxiety both preoperatively and postoperatively and thereby to aid her in dealing more realistically with her reactions. They will also provide information upon which to predict the intensity of the anticipated reaction. Evidence of deep-seated problems thus uncovered may suggest psychiatric consultation.

As far in advance of the operation as possible, the surgeon should plan a conference with the patient. At this time, he should offer her a brief but understandable statement of the procedure contemplated. His attitude should convey to the patient his own feeling of hopefulness and professional competence, but, at the same time, his explanation must be realistic. He should hope for and anticipate a normal emotional reaction with tears or expressions of fear, and he should allow the patient the opportunity to express these feelings fully. Following this, and worded as the circumstances and the particular nature of the patient dictate, certain questions should be asked. The patient's answers and reactions to these questions should be noted because they will reveal both conscious and unconscious reactions to the impending surgery.

At first one might say to the patient, "I wonder what you have heard about women who have had a breast removed?" This question provides the patient with an opportunity to voice fears, doubts and misconceptions that she would never admit as her own even though they are deeply disturbing to her. The patient's remarks will be an expression of her own optimistic or pessimistic outlook. It is to be expected, then, that the secure and self-confident woman will answer somewhat as follows: "Yes, I've known women who have lost a breast and they seemed to manage all right. It didn't seem to make any great change in their lives. As far as I could see, at least, they seemed to be the same as before." Contrast a reply of that type with the woman who says, "Yes, I know a woman who had a breast removed and she seemed to just close herself up in a shell. She stopped going out, she never saw friends, and the last I heard she was having all kinds of trouble."

Another question can be posed which will also give the woman a chance to express her thoughts and feelings in terms of another person. The surgeon may ask, "What will this operation mean to your husband?" The healthy woman answers somewhat this way: "I know he is greatly concerned for me, but I'm sure he feels confident, too. I suppose this will be difficult for him at first, but I have no doubt that his regard for me is based on more than the fact that I have one or two breasts." In opposition to this is the suspicious response from the patient who says, "I'm terribly afraid that this could mean the end of my marriage. I don't think my husband will be interested in a half-woman. I don't know if he could stand me that way." When the patient tells us what the loss of her breast will mean to her husband, one can be confident that her remarks are indicative of her own fears.

A third question, somewhat more direct than the previous ones, can then be raised: "How would you feel about having a breast removed? What would it mean to you?" The pathological answer can take two forms. On the one hand, a patient may blatantly state, "I would rather be dead than to have this operation." The other unhealthy form comes from the patient who denies any personal involvement, who professes the loss could not bother her a bit, who shows no apprehension. The more normal and expected will be one in which the woman voices a combination of concern and confidence, both of which are realistically oriented. She will express a realistic fear of the condition that requires such severe surgery, but she will also express the hopefulness which is characteristic of the well-adjusted person.

Finally, it is informative to ask the patient, "What steps will you take after the surgical scars have healed?" Again, the woman who has not been, or will not be, overwhelmingly threatened by the anticipated loss will respond in a positive manner. It is expected that she will indicate that she has given some thought to a prosthesis and sees the worth of this. She will be able to tell the surgeon that while a few new fashions may be impossible for her, she envisions no real difficulty in her ability to find and wear stylish, attractive clothes. The pathognomonic response to this interrogation is represented by the patient who hopelessly throws up her hands and says, "What steps can I take? After it's done, it's done. Once the breast has been removed, I'll no longer be a woman anyway."

The above is not meant to be an exhaustive description of what can and should take place in a preoperative interview. The surgeon is in a better position than anyone else to determine the general tenor and comprehensiveness of this kind of meeting. The authors' desire is to indicate that these questions, and other related ones, can serve as media through which the physician, first, gives comfort to his patient and, second, gains knowledge by which he can deal with the patient's responses in a helpful fashion.

There are a number of possible patient responses that may constitute pitfalls for the surgeon as he tries to evaluate the problem. Often what the patient does not say is more important than the verbalizations that do come forth. Some women will indicate an unwillingness to discuss these questions. They may put this on the basis of the futility of borrowing trouble—that they will adopt a wait-and-see policy—that they will face things one step at a time. Others will have you believe that this is something they can stoically accept — something they will take in stride. Such stoicism is the false calm overlying the subterranean storm. These are pathognomonic reactions. Since mastectomy and the possibility of malignancy are threatening and anxiety-producing to every woman, these last described reactions represent an unrealistic denial and avoidance of that which cannot realistically be denied or avoided. Persistent denial of feelings indicates the strong possibility of subsequent emotional pathology.

Some patients assume a passive and dependent role and, instead of dealing with these questions, throw them back to the surgeon by saying, "Well, I don't know doctor. What would you advise me to do?" In this instance, the doctor had better restrain his immediate impulse to be helpful and indicate to the woman that while he is willing to advise and help her, he would first like to hear how she feels and what she thinks about these things.

Some may protest that this recommended approach unnecessarily provokes unpleasant situations. It is suggested that the temporary unpleasantness thus occasioned is of far greater value to the patient than the avoidance of these areas by the physicians. Out of the empathy created by these discussions arise important insights for the surgeon. From these he can determine whether or not the personality of the patient is adequate to the stresses that will be experienced. He can perceive whether or not it is within his scope to deal with the intrapsychic disequilibrium born of his surgery or whether psychiatric consultation need be sought.

The things that make us anxious and afraid are those things we do not understand and those things which, for various reasons, we feel must be kept hidden in the darkest recesses of our minds. For all patients, the surgeon's willingness to deal openly and hopefully with the woman's fears, doubts, and uncertainties will go a long way toward mental equilibrium and an uncomplicated postoperative course.

Summary

Adverse emotional reactions to disfigurative surgery result from a disburbance of body image and self-concept. The surgical removal of an integral part of the body may disrupt the image of self to such an extent that the self can no longer function adequately in a social interpersonal sense. The breast is such an integral part and its removal can and may interfere with the female's ability to carry on in the feminine role. Two case histories serve to illustrate the effect of family environment and social factors in the genesis of self-concept and how mastectomy can alter this self-concept. The likelihood of postoperative emotional crises can often be detected by a brief but significant clinical assessment of the patient's reaction, both to the immediate threat of surgery and to postoperative plans. The patient's emotional concern may be expressed openly as a healthy anticipatory anxiety tempered with hopeful optimism, or veiled in various forms of denial and avoidance. Such evasions, as well as more grossly pathological reactions, require further explorations and perhaps preoperative psychiatric consultation. This approach may evoke criticism on the basis that it will cause unnecessary emotional turmoil in the patient but is justified by the empathy created, the insights gained, and the immediate possibility of avoiding postoperative crises.

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PATIENT PERSONALITIES

A physician must learn to recognize the personality traits of his patients and to guide his questions and evaluate the answers accordingly. A person who feels that you underestimate the severity of his symptoms or the gravity of his disease can often be "spotted" by the fact that he has pain or other symptoms anywhere you may suggest. It must not be forgotten, however, that these garrulous neurotics who often exaggerate or imagine irrelevant symptoms may also have serious organic disease—H. U. Hopkins, M.D., Ed., *Leopold's Principles and Methods of Physical Diagnosis. Third Edition.* 1965, p. 3.

A Simplified Method Of Colon Cleansing In Preparation For Sigmoidoscopy

Vincent A. DeLuca, Jr., M.D.

■ The value of routine sigmoidoscopy in detecting lesions in the sigmoid and rectum is receiving widening appreciation. Recent studies report rather striking uniform findings of approximately six per cent of unsuspected adenomatous polyps, and 0.2 to 0.3 per cent of unsuspected carcinomatous polyps, in a large hospital series[1] and a large office series[2] respectively. Cancer detection clinics throughout the country have reported incidences of polyps ranging from 2.5 per cent to 15 per cent following routine sigmoidoscopy, and an overall incidence of 0.22 per cent of rectosigmoidal carcinoma in asymptomatic patients.[3]

Almost 80 per cent of all cases of cancer in the colon and rectum are said to be within reach of the sigmoidoscope.[4] The instrument will detect 90 per cent of polyps in the rectosigmoid, as compared with about 25 per cent by roentgenography[5] and, as reported in one large series, less than three per cent by physical examination.

Failure to use routine sigmoidoscopy has been held responsible for "medical delay" in diagnosing cancer of the sigmoid and rectum, and a consequent significant increase in the stage of the disease before therapeutic measures were taken.[6]

Some proctologists consider that preparatory measures to evacuate the sigmoid and rectum are not necessary for sigmoidoscopic examination in many cases. Since the aim of the procedure is visualization of the lining of the bowel and rectum, however, we have found such preliminary cleansing generally essential for proper examination.

The following study was undertaken to evaluate the effectiveness of a standardized senna concentrate, in suppository form, in preparation of the sigmoid and rectum for sigmoidoscopy. Several reports in the literature[7-9] have indicated both the efficacy of this type of suppository and its acceptability to the patient.

Method And Materials

A study of standardized senna concentrate suppositories* in preparing the distal colon and rectum for sigmoidoscopy involved 156 patients, both hospitalized and in office practice; 88 were men and 68 women. Ages ranged from 10 years to 77 years, with an average of 48 years. Three patients were under 20 years and 15 were 65 years or older. Patients with either suspected or previous rectosigmoid lesions, or some gastrointestinal or anorectal pathology numbered 112, of whom 28 had chronic constipation. The rest were asymptomatic, and for them sigmoidoscopy was a routine part of a physical check-up. (Table I)

Hospital patients were administered one test suppository two hours before bedtime the evening before the procedure, and a second suppository in the morning, two hours before the procedure. Office patients were instructed to insert the suppositories at home, on the same schedule. The majority of the outpatients were able to administer the suppositories either at home or at the office without interrupting their routine work. Hospital personnel and private patients were requested to keep careful record of all bowel movements, including the time of response following each insertion and character of stool.

Results were evaluated as follows: Where there were no feces present to a distance of 25 cm. from the anorectal junction, the results were adjudged Excellent; where there were minimal feces present but not enough to interfere with visualization, the result was evaluated as Good; where there were

TABLE I
INDICATION FOR SIGMOIDOSCOPY

Routine examination	44
Irritable colon	30
Chronic constipation	28
Previous rectosigmoidol polyps	15
Hemorrhoids	11
Ulcerative colitis	9
Diverticulosis or diverticulitis	8
Proctitis	8
Anal fissure, anal papillitis	3
TOTAL	156

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* Senokot® Suppositories, supplied by The Purdue Frederick Company, Yonkers, New York.

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Table II
Visualization results following suppository administration

RESULTS	NO. OF PTS.	NO. INSERTIONS	NO. FOLLOWED BY BM'S	NO. WITH CHRONIC CONSTIP.
Excellent	69	137	131	5
Good	69	137	130	18
Poor	18	35	23	5
TOTAL	156	309	284	28
E + G = 89%				

sufficient feces present to interfere with visualization, irrespective of bowel movement, the result was evaluated as Poor. Note was also taken of the appearance of the mucosa to determine if there were alterations due to the suppositories, and of patient reactions.

Results

These are given in Table II. Visualization was excellent to good in 89 per cent of the series, with feces entirely absent in 45 per cent. In patients with constipation, visualization was excellent to good in 82 per cent, and a smaller proportion was completely free of feces than in the series as a whole.

The mucosal appearance was unaltered in 155 of 156 cases studied. The one case, involved a 46-year-old patient with an old rectal war injury and proctitis who had a history of many years of intermittent bleeding, a diffuse erythema coated with residual suppository material was observed.

The time of response and nature of stool are given in Tables III and IV. While 85 per cent of all insertions were followed by bowel movements within two hours, more than 95 per cent of the second day's insertions were followed by evacuation within that period, and the average time of response for this second suppository was half of that for the first. Ninety per cent had effective evacuations of soft and normal stools.

Side effects reported by patients included 14 cases of "cramps," of which only two were described as severe; eight, including the two described as severe were in patients with irritable colons or ulcerated colitis. There were 11 cases of rectal smarting, seven described as slight and the others unspecified as to severity; several of these were in patients with proctitis, oral fissure or prior rectal bleeding. Four patients complained of gas and one patient reported an uncomfortable feeling.

Table III
Time of response following suppository insertion; 156 patients

	NO. FOLLOWED BY BM'S	AVE. TIME OF RESPONSE	RESPONSE 1 HR. OR LESS	2 HRS. OR LESS (CUMULATIVE)
1st day's insertion	144	2.3 hrs.	55	109
2nd day's insertion	140	1.2 hrs.	85	134
TOTAL INSERTIONS	284	1.8 hrs.	140	243

Table IV
Nature of stool following insertions

	NO. BM'S	SOFT OR NORMAL STOOL	HARD STOOL	LOOSE STOOL
1st day's insertion	144	130	7	7
2nd day's insertion	140	128	3	9
TOTAL INSERTIONS	284	258	10	16*

* Nine of these were in patients with irritable colon, and alternating constipation and diarrhea.

Comment

A simple and effective method of preparing patients for sigmoidoscopy examination is discussed. Except for one patient in whom a slight eyrthema of the mucosa was noted, no effect of the suppository on the rectal mucosa of the patients studied was observed. Colon cleasing was excellent to good in 89 per cent of patients with or without colon disease or malfunction. The majority of outpatients were able to insert the suppository and subsequently continue their daily activities either at home or at work while awaiting bowel response. Hospital personnel time was considerably reduced with the use of suppositories compared to enemata.

Summary And Conclusions

The use of a standardized senna concentrate suppository in preparing patients for routine sigmoidoscopy was tested among 156 patients.

In 89 per cent, the sigmoid and rectum were either free of all feces, or contained a minimal amount permitting accurate visualization.

Side effects were minimal, and with few exceptions the suppositories were well accepted.

The method of colon cleansing described is a simple and effective technique for preparing patients for sigmoidoscopy. In hospitalized patients, it reduces personnel time, and in outpatients it allows the patient to continue normal activities while preparing for the examination. This simplified technique should encourage increased use of sigmoidoscopy examination.

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FURTHER INSTRUCTIONS FOR EXHIBIT, CONNECTICUT PHYSICIANS ART ASSOCIATION

April 25th, 26th, and 27th, 1967

As noted in the February *Journal,* all previous exhibitors are invited to show their works at this meeting and new exhibitors among physicians and their families are cordially invited to join the group of art hobbyists. Works eligible will include oil, water colors, tempora, black and white, etchings, photography, pastels, sculpture and ceramics. Eligible exhibitors are members of the Connecticut State Medical Society, their wives and children. Art works will be judged in four categories: 1. children through 16 years (over 16 will be judged with adults); 2. beginners to three years; 3. over three years; 4. professional.

A hanging fee of one dollar ($1.00) will be charged for each entry and fifty cents ($.50) for children under 16 with three pictures allowed per artist. Pictures should be framed and wired for hanging. The exhibition will be judged by professional artists. Art works must be submitted to representative of the Art Association in the lobby of the Statler Hilton Hotel, on Sunday, April 23rd, between the hours of 12:00 and 3:00 P.M. Art works cannot be accepted under any condition after April 23rd, since the exhibit list will be made up at that time.

Members of the Art Committee or their representatives will be in attendance at the displays throughout the exhibit at the state meeting. The Connecticut State Medical Society (nor the Art Association) can assume no responsibility for loss or damage of any cause whatsoever, to such art works.

The art works may be picked up between 12:00 and 4:00 P.M. on Thursday, April 27th. Paintings over 24 x 30 inches will be hung only upon discretion of the art committee.

Make checks payable to Connecticut Physicians Art Association and forward to me at the below address before April 15th. Any questions may be directed to me also at this address.

Stewart J. Petrie, M.D.
President, Connecticut Physicians Art Association
56 Minerva Street
Derby, Connecticut 06418

FROM THE GENERAL MANAGER'S OFFICE

William R. Richards, m.d., *General Manager*
160 St. Ronan Street, New Haven, Conn.
Telephone 865 0587

Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

CALL

ANNUAL MEETING OF THE HOUSE OF DELEGATES

The 1967 Annual Meeting of the House of Delegates will be held at the Hartford-Hilton Hotel, Hartford, commencing at 9:00 o'clock in the morning of Tuesday, April 25.

Following luncheon, the House will reconvene for the completion of business.

Orvan W. Hess, President
Kenneth F. Brandon, Speaker of the House
Waldo E. Martin, Secretary

INTRODUCTION OF RESOLUTIONS

Article V, Section 12, Par. 3 of the Bylaws of the Society Provides that:

All resolutions to be considered as regular business at any regular meeting of the House of Delegates must be in the hands of the Speaker not later than seventy-two hours before the opening of that meeting. All resolutions and recommendations published in the official agenda distributed to the members of the House prior to the meeting at which action is to be taken shall be considered as regular business. Resolutions presented later than seventy-two hours before the opening of a meeting will be referred for consideration as regular business by the House only when they are presented by the Council or accepted for consideration by majority vote of the delegates present. Any resolution which does not qualify in accordance with the aforesaid provisions for consideration as regular business may be accepted for action by a majority vote of the delegates present and, if so accepted, shall be referred at once by the Speaker to a reference committee. Any such reference committee shall consider resolutions referred to it and shall report, with recommendations to the House before adjournment of the meeting.

PROPOSED AMENDMENT TO THE BYLAWS

The following proposed amendment to the Bylaws was presented to the House of Delegates on December 8, 1966 and were tabled for consideration and action at the next regular meeting of the House of Delegates.

In accordance with the Bylaws, this amendment will be published in Connecticut Medicine, "on one or more occasions prior to the next meeting . . . at which meeting the amendment shall be taken off the table and acted upon by the House of Delegates."

INTRODUCED BY THE COUNCIL:

The Committee(s) On Public Relations

Objective: To abolish the present two-committee PR Divisional structure (totalling 19 members) and to provide for the annual election of a single large committee of 24 members. By so doing, it is hoped to increase the effectiveness of the PR Division by having more participants numerically; to assure having adequate county-by-county representation at all meetings of the Division; and to stimulate greater interest in public relations activities at state and county levels through a continuing two-way exchange of ideas.

Proposed Amendment: Article XI—DIVISIONAL BOARDS AND COMMITTEES.

(I) Section 3.—Divisional Standing Committees

Par. (E)—Public Relations Division

Delete: Committee on County and Local Public Relations. Committee on State and National Public Relations

Substitute: Committee on Public Relations

(II) Section 5.—Duties of Standing Committees

Delete: Present Paras. 16 and 17 (describing present 2 committees)

Substitute: New Par 16 as follows:

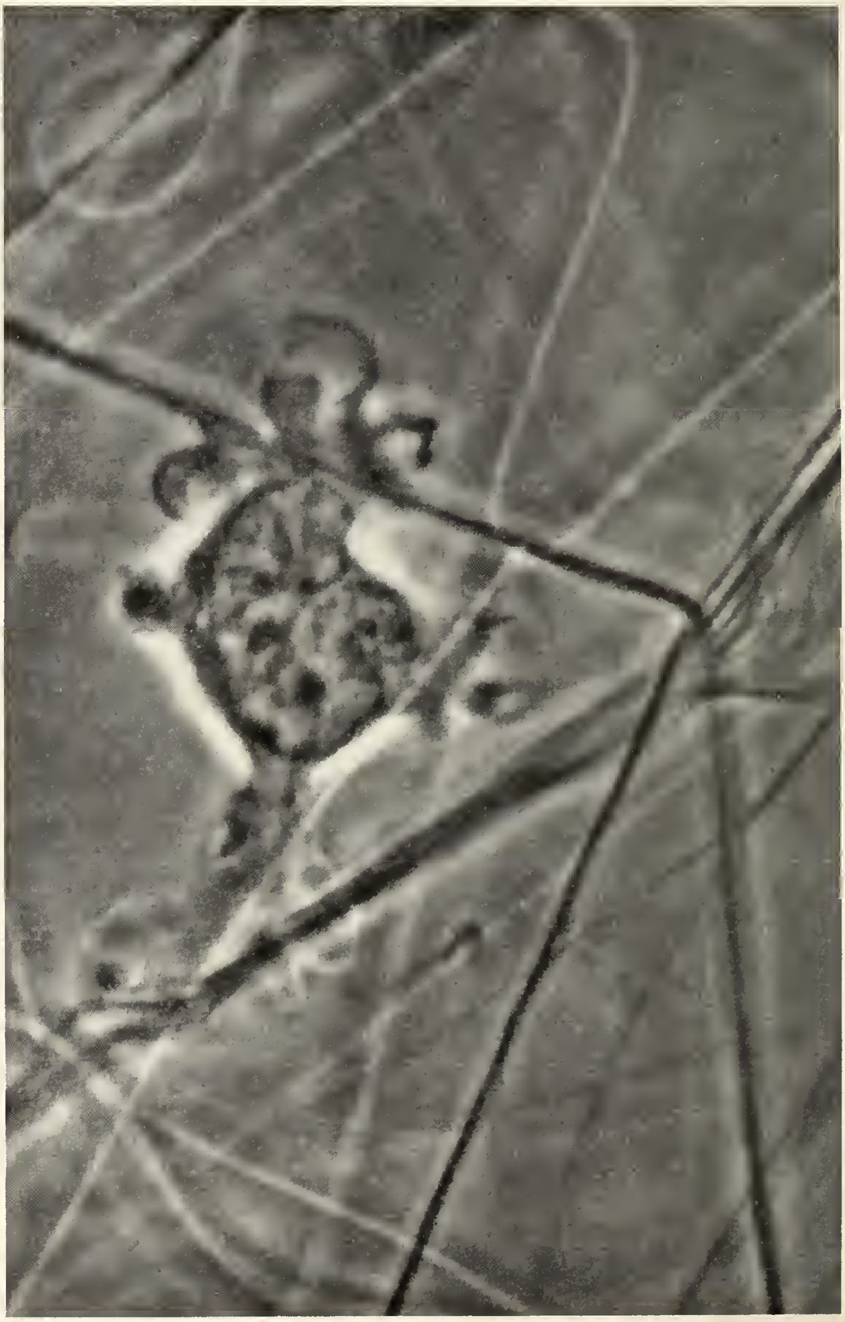
Par. 16 COMMITTEE ON PUBLIC RELATIONS. The Council shall annually nominate to the House of Delegates a Committee on Public Relations of twenty-four members of The Society and shall nominate the chairman thereof. The nominations shall be made as follows: Eight members recommended for nomination by the component county medical associations, on the basis of one per county; eight additional mem-

INFLAMMATION:
A cellular fight for life

A SYNTEX REPORT based on recently developed hypotheses about topical corticosteroids, including the cellular theories of inflammation by Thomas F. Dougherty, Ph.D., University of Utah.

You are looking at a fibroblast fighting for life. This cell – one of the most common found in connective tissue – has literally been poisoned by cytotoxins released from other cells that have ruptured. Soon, if the abnormal activity of this fibroblast does not cease, it, too, will rupture and die – one more casualty in the inflammatory wave of destruction precipitated by injury.

Until a short time ago no one had ever witnessed such a scene at the cellular level. Now, through advanced cinemicrographic techniques, it is possible to view and photograph the inflammatory process as produced experimentally in living animal tissue. This method permits new insight into the mechanism of inflammation and the role of corticosteroids in therapeutic management. Equally important, these techniques shed new light on factors that may make one corticosteroid more effective than another – factors that can be correlated with other chemical, biologic, and clinical parameters.



Worldwide clinical experience confirms the predictable therapeutic potential of Synalar

It is particularly gratifying that the promise of the advanced chemical design and high order of bioassay activity of Synalar (fluocinolone acetonide) has been confirmed by widespread therapeutic application. Indeed, the impressive clinical response rate of Synalar has been documented in no fewer than 232 papers from 22 countries.

Representative Clinical Results with Synalar*

Efficacy Documented in over 4,000 Patients

Condition	Number of Publications	Number of Patients	Significant Improvement†
Contact Dermatitis	27	750	713
Eczematous Dermatitis	21	472	409
Seborrheic Dermatitis	18	442	426
Atopic Dermatitis	24	460	426
Psoriasis	36	1,699	1,510
Neurodermatitis	18	351	324
Total	144	4,174	3,808

*Complete bibliography on request.

†Expressed by the authors as excellent, very good, good, complete remission of inflammation, etc.

PRESCRIBING INFORMATION
For initiation of therapy: Cream 0.025%, 5 and 15 Gm. tubes, 425 Gm. jars; *for emollient effect:* Ointment 0.025%, 15 Gm. tubes; *for maintenance therapy:* Cream 0.01%, 15 and 45 Gm. tubes, 120 Gm. jars; *for intertriginous or hairy sites:* Solution 0.01%, 20 cc. and 60 cc. plastic squeeze bottles; *for infected inflammatory dermatoses:* Neo-Synalar® Cream (0.025% fluocinolone acetonide, neomycin sulfate, equivalent to 0.35% neomycin base), 5 and 15 Gm. tubes.
CONTRAINDICATIONS: Tuberculous, fungal, and most viral lesions of the skin, (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. PRECAUTIONS: Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Prolonged use of any antibiotic may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy should be instituted. When severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. SIDE EFFECTS: Side effects are not ordinarily encountered with topically applied corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. The neomycin in Neo-Synalar Cream rarely produces allergic reactions.

REFERENCES: 1. Lerner, L. J., Bianchi, A., Turkheimer, A. R., Singer, F. M., and Borman, A.: Anti-inflammatory steroids: potency, duration and modification of activities. Ann NY Acad Sci 116:1071 (Aug. 27) 1964. 2. Idem: Comparison of anti-granuloma, thymolytic and glucocorticoid activities of anti-inflammatory steroids. Proc Soc Exp Biol Med 116:385 (June) 1964. 3. Ringler, A.: Activities of adrenocorticosteroids in experimental animals and man, in Dorfman, R. I.: Methods of hormone research, New York, Academic Press, 1964. vol. III. pp. 234-280. 4. Gubersky, V. R.: To be published.

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For inflammatory
dermatoses...
by any measure
a topical corticosteroid
of choice

Synalar®
(fluocinolone acetonide)

Milligram for milligram one of the most active topical corticosteroids available

Rapid and predictable in antiinflammatory and antipruritic activity

Results often comparable to those of systemic corticosteroids with fewer hazards

bers selected by the Council, on the basis of one from each county; and the other eight members to be selected at-large. The function of the Committee shall be to inquire into and pass upon such phases of public information as deal with the care of the sick and the practice of medicine, to keep the people of Connecticut accurately and reliably informed concerning matters of public interest in the field of medicine, to encourage cordial relations and understanding with communications media and to cooperate with other committees of the Society and of the AMA in a program of public relations. The Committee shall assist the committee on public relations of the component associations in developing and disseminating accurate and reliable information concerning matters of public interest in the field of medicine and shall use its efforts to encourage cooperation by the committees on public relations of the component associations with local medical societies, allied professional groups, voluntary agencies, the press, radio, television and other groups within the respective counties in a program of public relations.

(III) Renumber present Paras. 18 through 29 to become Paras. 17 through 28.

SUMMARY OF ACTIONS COUNCIL MEETING

Thursday, February 16, 1967

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Hess, Bradley, Gardner, W. Martin, Goldberg, Brandon, M. Caplan, Fabro, H. Caplan, Polivy, Rogol, Grendon, Egan, Abbot, Shepard, Ayres, Nolan, Cramer, Petrie, Pelz and Roch. Also present were: Mrs. Lindquist, Mr. Villano, Mr. Chilcoat (AMA), and Dr. Richards.

Absent were: Drs. Spitz, Hastings, Ciccarelli, Grant, Wilson and Palomba.

II. Routine Business

Approval Of Minutes

As printed and distributed, it was VOTED to approve the minutes of the meeting of January 11, 1967.

Life Memberships

It was VOTED to approve applications for life Membership received from eligible Active Members of the Society as follows:

B. J. Borkowski, Bristol (HCMA), 1967
Philip Carroll, Bridgeport (FCMA), 1967
Muriel Case Downer, West Hartford (HCMA), 1967
Isidore S. Geetter, Hartford (HCMA), 1967
J. J. Goldenberg, Hartford (HCMA), 1967
James J. Hennessey, West Hartford (HCMA), 1967
Raymond S. Holtz, Hartford (HCMA), 1967
Albert E. Levin, Hartford (HCMA), 1967
H. M. Marvin, New Haven (NHCMA), 1967
Philip F. Parshley, West Hartford (HCMA), 1967
Rocco J. Romaniello, Elmwood (HCMA), 1967
Louis G. Simon, Norwalk (FCMA), 1967
John W. Suplicki, Norwich (NLCMA), 1967
William A. Wilson, Hartford (HCMA), 1967

Election Of Student Members

It was VOTED to elect to Student Membership the following Connecticut residents who are attending U.S. schools of medicine:

Thomas W. Glynn, Burlington Road, Unionville
University of Kentucky—Class of 1967
Pre-Med: University of Connecticut
Parent: James Glynn

James Robert Missett, 1790 Boulevard, West Hartford
Yale University—Class of 1970
Pre-Med: St. John's University
Parent: James S. Missett, M.D. (deceased)

Appointment To Advisory Committee— Home Health Aide Training Project

In response to a request from the State Health Department, it was VOTED to appoint Norton G. Chaucer, Hartford, as a CSMS representative to serve with the Advisory Committee to this Project. Using an Office of Economic Opportunity grant, the project will make plans to train "home health aides" for employment by non-profit, community agencies offering homemaker services in the State.

Date Of Next Meeting

The next meeting of the Council will be held on Wednesday, March 15, 1967.

III. Old, New And Special Business

1967 Annual Meeting

Dr. Polivy, Dr. Hess and others brought it to the Council's attention that the April 25-27 dates of the Annual Meeting this year will fall, in part, during the Passover Holidays. There was unanimous agreement that the conflict represented an entirely unintentional oversight on the part of the Council, in setting the dates for the meeting last summer, and it was VOTED to acknowledge the oversight to the membership in a statement to be published in the Journal. In the future, special efforts will be made to eliminate the possibility of this or similar conflicts coming about.

Request—Connecticut Regional Medical Program Planning Committee

Dr. Henry T. Clark, Jr., Planning Director of the CRMP, joined the Council to request the Society to recommend interested and qualified members of the Society to the CRMP Planning Committee for appointment to service with the nine "Task Forces" which are being organized to study special segments of the areas to be covered in the planning of a Regional Medical Program. Following Dr. Clark's presentation, and a period of questions and answers, it was VOTED to authorize the President, the Chairman of the Council, and the General Manager, seeking whatever consultation with others they may consider to be desirable, to recommend 2-4 members of the Society for appointment to each of the Task Forces in which the Society has an interest. It was suggested that the rosters of pertinent CSMS committees having to do with the subject areas might be used as basic "pools" for the selection of suitable nominees.

Report—Ad Hoc Subcommittee On Council Survey Questionnaire

It was VOTED to accept, with commendation, the report of the Subcommittee, presented by Orvan W. Hess, Chairman, but to disapprove a recommendation that an "advisory subcommittee on agenda" be established to make a detailed prior review of the agenda. In brief, the balance of the report made recommendations concerning the frequency of Council meetings (every four weeks); their regularity (the second week of each month, barring major conflicts; alternating between Wednesdays and Thursdays); their length (a limit of four hours, unless the Chairman obtains majority consent to continue); and their starting time (2:00 P.M., except for special occasions).

Report—Conference Committee With The Bar Association

William J. Watson, New Britain, Chairman of the CCBA, and Averill A. Liebow, New Haven, a member of the Committee, joined the Council to present and explain the "Medicolegal Investigation Act" which was developed jointly by the attorneys and physicians serving on the Conference Committee, and which has been formally filed with the 1967 General Assembly for action. In brief, the legislative proposal would establish a medicolegal investigations commission in Connecticut, and, under the commission's direction, set up an office of medicolegal investigations with a chief medical examiner, deputy medical examiners, and staff. The adoption of this proposal by the General Assembly would institute the "medical examiner" system in the State, and would gradually "phase out" and eventually replace the present coroner system. Following the presentation made by Drs. Watson and Liebow, the Council VOTED to approve the provisions and purposes of the act, and to request them (Watson and Liebow) to appear as CSMS representatives at the proper committee hearing to testify in support of it.

Report—Subcommittee To Study And Revise The Bylaws

(a) It was VOTED to adopt the amendments to the Bylaws recommended by the Subcommittee which are necessary to establish the "Judicial Committee", proposed by the Committee on Preliminary Study of Censorship Questions and approved by the Council, and to transmit these amendments to the House of Delegates on April 25 for appropriate action.

(b) It was VOTED to approve the report of the Subcommittee, which defined a "member under suspension" as being still a "member" at both CSMS and county medical association levels; which defined the minimum loss of "rights" while under suspension to be those of voting and holding office, at both state and county levels; and which recommended that payment or non-payment of dues while under suspension be a requirement left to the decision of the separate organizations concerned.

Report—Committee On Public Health

It was VOTED to approve, in principle, a resolution offered by the Committee which proposes that the Society urge physicians to take a greater interest in problems of teenagers (venereal disease, out-of-wedlock pregnancy, etc.), and that the Society undertake to plan and conduct (sponsor) courses for physicians at state and county level in these subjects; conferences of physicians and school authorities on same; and establish a medical advisory committee on family living, sex education, etc. It was further VOTED to request the Committee on Public Health to study and report on specific plans for implementing the several parts of this resolution, including personnel, course and conference formats, and estimates of costs.

Report—Liaison Committee With Connecticut General On Medicare B

The minutes of the liaison meeting of January 30 were presented in printed form, and were enlarged upon by Dr. Polivy (who acted as Chairman for the CSMS component). Following discussion of the various matters presented, it was VOTED: (a) To refer to the Committee on Third Part Payments for study and report the problem of trying to define the relative values of various types of physician visits to patients in extended-care facilities (emergency, prolonged attendance, routine, etc.), and to make recommendations as to how these values could be applied practically by Connecticut General in processing claims for payment; (b) To request the CSMS component of the liaison group to prepare a summary of the matters discussed at the several meetings with Connecticut General thus far for publication as information to the membership and for distribution to the members of the Committee on Medicare-Medicaid Experience.

Second Conference Of County Medical Association Officers

It was VOTED to have the officers of CSMS (and staff) plan and conduct a second conference of county medical association officers, on or before the middle of March, and to prepare a suitable agenda for same. Some of the items to be brought before the Conference are: The new format for the annual meeting of the House of Delegates; the findings of the first Conference; a report on hospital-physician financial arrangements; and a discussion of the future of the Journal, financial and otherwise.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on February 16, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT WANTED

G.P.—30 years of age, military obligations completed. Wishes to practice with either a group or an associate in the Guilford area.

INTERNIST—33 years of age, Board eligible, military obligations completed. Wishes to practice with a group in a medium to small community.

SURGEON—31 years of age, Board eligible, military obligations completed. Interested in a practice of general and/or thoracic and peripheral vascular surgery with a group or an associate. Native of Connecticut.

PLACEMENT OPPORTUNITIES

RADIOLOGIST—350-bed general hospital needs third radiologist for general diagnostic work. Isotopes, therapy and special procedures available, if interested. A new 9-room department is being built. Salary $25,000 with yearly increments. Contact: Howard F. Root, M.D., c/o Department of Radiology, New Britain General Hospital, New Britain, Connecticut 06050.

OBS-GYN—Board certified Obs-Gyn needed to associate with another Obs-Gyn in large industrial city in Southern Connecticut, leading to eventual partnership.

HEALTH DIRECTOR—City of Stamford, population 100,000 needs physician with a degree in Public Health, with administrative experience, and willing to assume leadership in expanding and coordinating the health activities of a community, can command salary equal to or higher than any in the area. Contact: Frank H. D'Andrea, M.D.; Chairman, Health Commission; 750 Summer Street; Stamford, Connecticut 06902.

Physician with a background in internal medicine and/or pediatrics who is interested in a group practice in a rural town in Southern Connecticut. Hospital services available at several area hospitals.

PHYSICAL MEDICINE & REHABILITATION—Vacancy for Senior Physician with training and experience in physical medicine and rehabilitation. Fully equipped department with occupational, physical, speech and educational therapy units and photography laboratory in 496 bed state veterans hospital. Foreign graduate—ECFMG required. Three weeks vacation, sick leave with pay, hospitalization, Group Life Insurance and other benefits. Salary range: $13,040-$17,040 per year, rate commensurate with level of training and experience. Write: Personnel Officer, Veterans Home and Hospital, Rocky Hill, Connecticut.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

Welcome New Members . . .

Middlesex County Medical Association

Donald P. Buebendorf, M.D. — Middlesex Turnpike, Centerbrook, Connecticut 06409

Richard M. Campbell-Jacobs, M.D. — 45 Crescent Street, Middletown, Connecticut 06457

Malcolm Gorin, M.D. — 40 Broad Street, Middletown, Connecticut 06457

Arthur L. Waldman, M.D.—40 Broad Street, Middletown, Connecticut 06457

1967 MEETINGS

April 25-27—175th ANNUAL MEETING of the Connecticut State Medical Society to be held at the Hartford-Hilton Hotel, Hartford, Connecticut.

WOMAN'S AUXILIARY

President
Mrs. John D. O'Connell, West Hartford

President-Elect
Mrs. Anthony Cipriano, Hamden

First Vice-President
Mrs. Henry Sherwood, Middletown

Second Vice-President
Mrs. Edward P. Allen, Orange

Recording Secretary
Mrs. Nicholas Creaturo, Trumbull

Corresponding Secretary
Mrs. Irving H. Krall, West Hartford

Treasurer
Mrs. Forest D. Gibson, Farmington

Reminder—The Annual Meeting of the Woman's Auxiliary to Connecticut State Medical Society April 24 at 42 Fulton Place, West Hartford, 2:30 p.m., the program will include Mrs. Paul Rauschenbach, Director of the Woman's Auxiliary to the A.M.A. Mrs. Rauschenbach is a most interesting and charming person, having held many chairmanships on the National Board. We hope to see many of our members to honor her and especially our outgoing president, Mrs. John D. O'Connell.

1967 Convention

Atlantic City, New Jersey

June 18 to 22

The following is a brief listing of activities to enable you to plan your schedule:

Friday, June 16: Finance Committee meeting, 9:00 a.m.

Saturday, June 17: Meeting of the Board of Directors, 9:00 to 5:00 p.m. National chairmen and National representatives to meetings (auxiliary and others) are invited to attend the afternoon meeting to give brief reports. Board of Directors Luncheon, 1:00 p.m. Guests will be National Board, National Chairmen, Past Presidents and Honorary Members.

Sunday, June 18: Meeting of the National President-elect, Mrs. Karl F. Ritter, with the 1967-68 Chairmen, 9:00 a.m. Resolutions Committee meeting, 10:00 a.m. Registration will open at 11:00 a.m. Hospitality Room will open at 11:00 a.m. Coffee will be served until 1:00 p.m. Reception, honoring the National President and President-elect, will be held from six to eight o'clock at the Shelburne Hotel. Opening Meeting of the AMA House of Delegates. (Consult AMA program for time and place). AMA Medicine and Religion Program, 8:00 p.m., Auditorium, Convention Hall (Civic Center).

Monday, June 19: Formal opening of the convention, 9:00 a.m. to 12:15 p.m. and 2:30 to 4:30 p.m. Guest Day Luncheon for leaders of National Women's Volunteer Organizations, Auxiliary members and guests, 12:30 p.m., Ballroom, Shelburne Hotel. Guest speaker to be announced.

Tuesday, June 20: Presentation of state reports with the National vice presidents participating (continued from Monday). Dr. Mary Calderone, Executive Director of SIECUS, will speak on "Sex Education—Goals and Means." Annual luncheon—Guest speaker: Dr. Charles L. Hudson, President, American Medical Association. *Little Workshop*—2:30 to 3:30 P.M. Two way discussion between state presidents, presidents-elect and National officers and committee chairmen. Delegates invited. Questions and topics for discussion may be placed in question box during convention. POLITICAL ACTION PROGRAM, 3:30 to 4:30 P.M. Joint discussion by Auxiliary legislative leaders and women's international representative. Polls will be open for voting from 2:30 to 6:00 P.M.

Wednesday, June 21: General Meeting—9:00 a.m. to Noon. Amendments, resolutions, reports and installation of the new officers will follow. Board of Directors meeting 12:15 p.m. Meeting with 1967-68 Chairmen 2:30 p.m.

Thursday, June 22: Postconvention Conference for Presidents and Presidents-elect, (open to all Auxiliary members). 9:00 a.m. to 12:15 p.m. Presentation and discussion of 1967-68 programs and projects. AMA Round-Up—Ernest B. Howard, M.D. Asst. Exec. Vice President, American Medical Association.

There will be no Friday meetings. Reservations should be made on the official form in the March issue of MD's Wife and mailed to the AMA Housing Bureau, 16 Central Pier, Atlantic City, New Jersey 08401.

NEW BOOKS IN REVIEW

CONFLICT IN SOCIETY: Ciba Foundation Symposium. Edited by Anthony De Reuk and Julie Knight. Little Brown and Company, Boston, Massachusetts. 467 pp., 15 contributors. $13.00.

Reviewed by: LOUIS H. NAHUM

With this symposium The Ciba Foundation famed the world over for its contributions to the biomedical sciences has gone somewhat far afield in an attempt to offer some insights into the causes and the processes of social conflict. Aggression in the animal world is considered and the psychological and sociological processes which lead men into conflict are considered by world famous authorities drawn from many disciplines such as history, international law, behavioral sciences including psychiatry, and even systems analysis. Conspicious by their absence were scholars representing the Marxian doctrine of the origin of wars among nations. This ommission might be attributed either to a bias against this view by a Capitalist Foundation or a belief that no new insights have been produced by the Marxian group to shed further light upon war.

We are therefore left with a view that man being the only species that wages war on his own kind does this because, armies raised to engage in conflict are made up of individuals whose aggressiveness is channeled into the service of those in governments who determine when and whom to fight.

All agreed that it is necessary to distinguish between a nation that agresses against another as the Germans did and the people of the attacked nation who as a result are either forced to defend themselves, be destroyed or surrender. There was discussion about national idealogies with the employment of such emotive words as "Freedom", Democracy", "Aggression" and the general recognition that such slogans often hide the real motives of those who determine the foreign policy of a nation. They recognized that Nazi Germany mobilized its masses with such and similar slogans and threw its armies against Poland after accusing the Poles of "Aggression". All felt one must go behind the slogan to understand the real purposes of those who use them.

What the reader was left with was that at present at least in the western world political theory is not a well-integrated field and does not seem well oriented towards the goals which are beginning to emerge in the minds of scholars. Professor Karl Deutsch, one of the participants, eloquently stated such goals elsewhere as a political theory for peace, a more adequate theory for political and economic development which would avoid chaos and oppression, and strive to preserve and enhance human life and freedom. A third problem was that of finding a political theory for the "self-transforming" society, leading to greater abundance for all and to ever greater freedom for each individual.

Much of these goals were implied in what the participants in this symposium thought, but unhappily they produced no theories, models or direction adequate for attainment of these goals.

A MANUAL OF TROPICAL MEDICINE, 4th Edition. Edited by George W. Hunter, III, Ph.D., Col. U.S.A. (ret.), William W. Frye, Ph.D., M.D., Sc.D. (Hon.) and J. Clyde Swartzwelder, Ph.D. W. B. Saunders Company, Philadelphia and London, 1966. 871 pp. with 323 illustrations, 8 in color.

Reviewed by: LOUIS H. NAHUM

This superb volume will contribute to the best levels of medical practice in the tropics and subtropics and will prove a boon to the student, medical officers in the field and physicians in practice at home. The value to the physician at home is brought forcibly to our attention by the importation into this country from South Viet Nam of clinical cases of malaria due to resistant falciparum strains in the form of malignant cerebral malaria.

The first edition of this book was prepared for our armed forces during World War II. It stressed both epidemiological and clinical aspect and became at once a text book for medical and graduate students, clinicians as well as for medical personnel in medicine, public health, microbiology and allied fields.

New medical problems have arisen, such as resistant malaria, certain viral and other infectious diseases, and have required a new edition. In the book we find pertinent information on the major infectious diseases, nutritional disorders and other conditions which constitute the important health problems in the tropics. To be sure many of these diseases are also endemic or have their biologic analogs or epidemiologic counterparts in the temperate zone as well as in the tropics and subtropics.

Because tropical medicine has such a broad expanse and includes so many diseases and specialties, the authors have recruited thirty-seven special contributors of outstanding merit, individuals recognized for special knowledge and for basic research on specific fields. There is a section on laboratory diagnostic methods and procedures, an appendix which presents the distribution of selected communicable diseases in the tropical and subtropical areas of the world.

The book is whole page print, excellent type, fine paper and beautiful figures. It is a superb volume with a wealth of information and ideas and will be widely used as a text of Tropical Medicine.

GERIATRIC PSYCHIATRY. Grief, Loss, and Emotional Disorders in the Aging Process. The Boston Society for Gerontologic Psychiatry, Inc. Edited by Martin A. Berezin, M.D. and Stanley H. Cath, M.D. International Universities Press, Inc., New York. $7.50.

Reviewed by: STEPHEN FLECK

This unusual volume is rich and varied in its contents for its size and price. It includes in three parts, the presentations at the second and third annual meetings of the Boston Society for Gerontological Psychiatry. These are respectively, the first and second sections, and Part III is a critically an-

"George wants to know if it's okay to take his cold medicine now, Doctor, instead of seven o'clock?"

The long-continued action of Novahistine LP should help you both get a good night's sleep. Two tablets in the morning and two in the evening will usually provide round-the-clock relief by helping clear congested air passages for freer breathing. Novahistine LP also helps restore normal mucus secretion and ciliary activity—normal physiologic defenses against infection of the respiratory tract. Use cautiously in individuals with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution ambulatory patients that drowsiness may result. Each Novahistine LP tablet contains: phenylephrine hydrochloride, 25 mg., and chlorpheniramine maleate, 4 mg.

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notated bibliography by Dr. Robert S. Moss, of 117 psychiatric publications on aging from 1950-1960. This last section alone is of great value.

The first two sections suffer from the usual dilemma of fitting together expert presentations prepared for conference and discussion into a coherent and sequential written format. In this the book fails despite the excellent introductions by the editors. The subtitle Grief, Loss, and Emotional Disorders in the Aging Process is very apt for all presentations although it is used as a heading for only the first symposium. The list of authors is impressive and they all live up fully to their reputations. That the book does not become an integrated whole is not a deficiency of these separate papers, and maybe reflects the current state of psychiatric gerontology, a field to which very few psychiatrists and psychoanalysts have devoted so far the major share of their professional energy and attention. As a resource for specific topics and problems of aging people the book is highly recommended.

HEMATOLOGIC PROBLEMS IN THE NEWBORN. Edited by Frank A. Oski, M.D. and J. Lawrence Naiman, M.D. Vol. IV in the Series Major Problems in Clinical Pediatrics. Alexander J. Schaffer, Consulting Editor. W. B. Saunders Company, Philadelphia and London, 1966. 294 pp.

Reviewed by: S. C. FINCH

This book is an excellent compilation of hematologic information, that usually is most difficult to locate without consulting a wide variety of references. The first two chapters are devoted to the profound hematologic adjustments, which occur during the prenatal and neonatal periods. The magnitude and rapidity of these changes is such that this succinct and well organized presentation of the normal hematologic values alone is of considerable reference value. The remainder of the book describes both hematologic disorders which are peculiar to the newborn and the unusual newborn features of hematologic illnesses which occur at any age. Each subject is introduced with a brief discussion of pathogenic mechanisms which include related genetic factors. Diagnosis and treatment are clearly outlined. Numerous summary tables, schematic diagrams, current references and a few microphotographs give first class support to the text. Some of the tables and figures, however, suffer from small print size, a rare inaccuracy and unnecessary detail. Despite these minor criticisms, the book is highly recommended. It should be particularly useful to pediatricians and hematologists.

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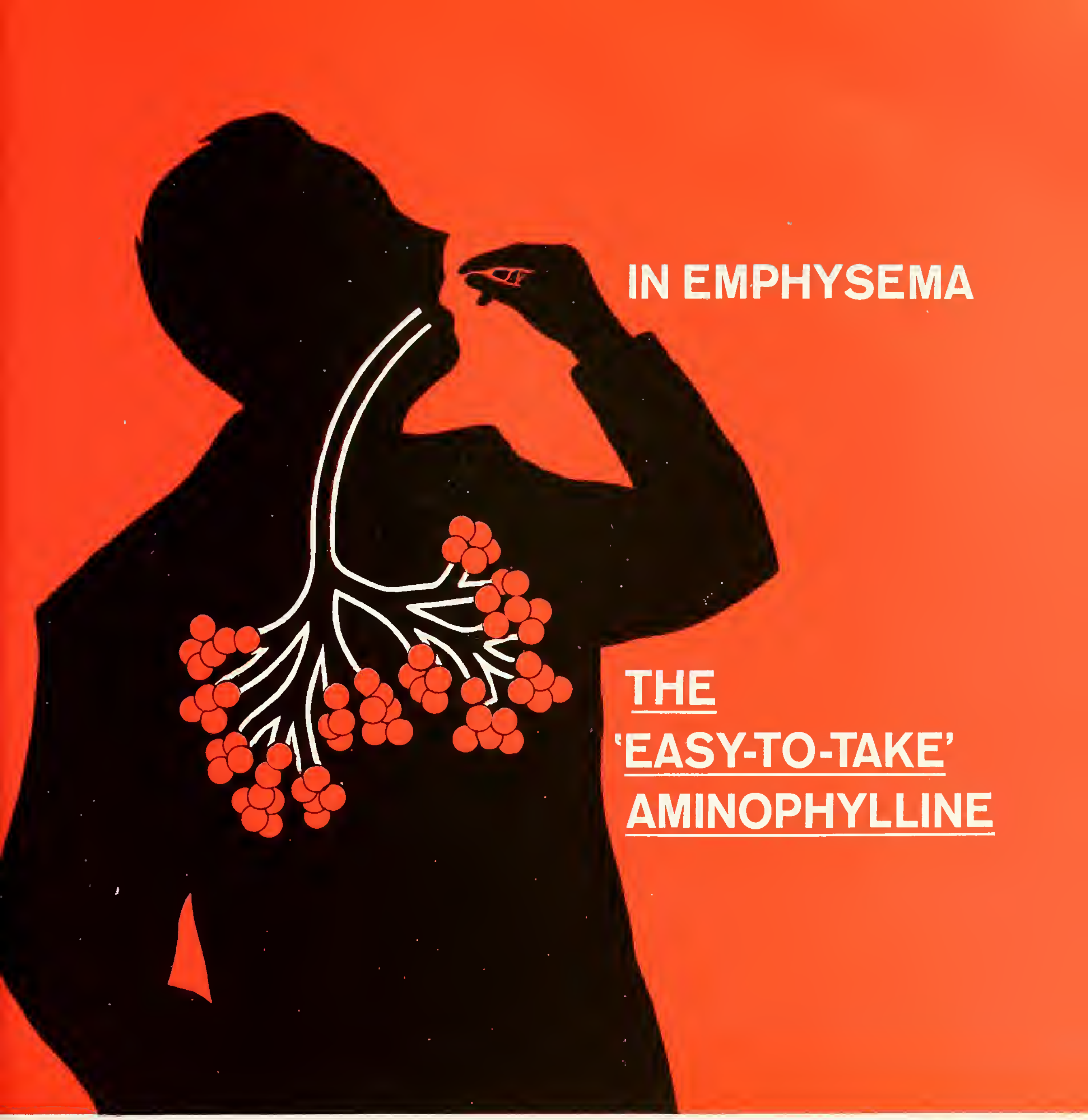

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Connecticut State Medical Journal

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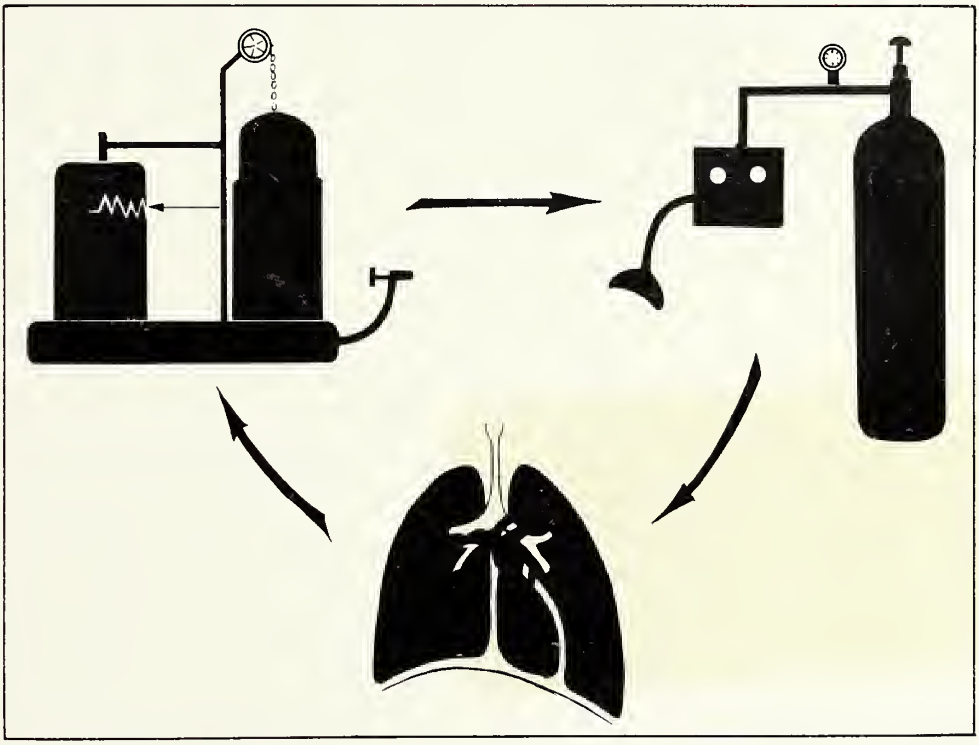

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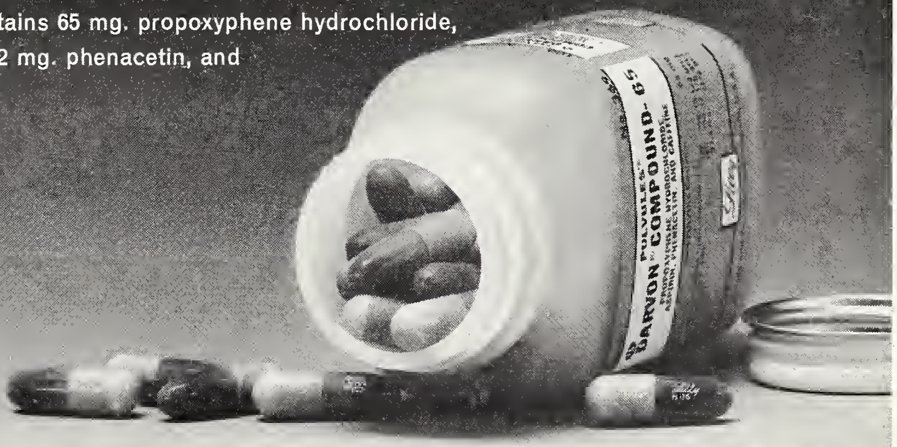

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Connecticut Medicine

editorials

Dr. Fredrick C. Redlich New Dean Of Medicine At Yale

Dr. Redlich, chairman of Yale's Celebrated Psychiatry Department and Director of the Connecticut Mental Health Center has been appointed Dean of the Yale School of Medicine effective July 1st. Dr. Redlich born June 2nd, 1910 in Vienna and a refugee from Hitler's tyranny will become the 10th Dean of the Yale School of Medicine succeeding Dr. Vernon W. Lippard who has been Dean since 1952. President Brewster in commenting on the appointment said, "Dr. Redlich deservedly enjoys the highest respect of practitioners, of clinical investigators and of medical scientists. Under his leadership Yale will have a great opportunity to make a distinctive contribution to the training of sophisticated physicians and to the advancement of the art and science of medicine".

Two parallel trends in medical education and medical practice are about to converge under the leadership of the new Dean. One is the drive to expand biomedical science begun by Abraham Flexner in 1910 which led to a complete reorientation of medical school faculties towards full time investigators and teachers. This philosophy was introduced into Yale by Dean Milton Winternitz in 1920 and now Yale can be proud of a faculty of outstanding scientists who have and are continuing to add to the sum of biomedical knowledge.

A second trend is towards the recognition of medical practice as directed towards a human being who is sick. But a sick person is not alone unto himself. He is a part of a household, which is a part of a community which is a part of society. In short medicine is also a social activity. The scientific revolution in medicine is advancing rapidly towards the solution of many unsolved problems including genetic and environmental factors. There is also a psychologic revolution in progress which brings man, his mental and emotional components into focus. We are learning how to cure sometimes, to relieve often. Now in Dr. Redlich's view we must learn how to comfort always. Actually this has been the stock in trade of every practicing physician. The expansion of medical science has only temporarily diverted attention from the person to his sickness. We are now about to go back to the sick human being in the age old tradition of Medicine.

In fact this idea of medicine as a science and art and as a social activity was already anticipated by Dean Winternitz who together with Robert Hutchins, Dean of the law school induced the Rockefeller Foundation in the early 1920's to build an Institute of Human Relations. The idea was right but the time was wrong—which incidentally attracted Dr. Redlich to New Haven. The Institute had little impact on the Medical School. A development where scholars from the behavioral sciences and public health could co-operate with biomedical scientists to expand our knowledge of human behavior and man's relation to his environment became possible only more recently. At Yale the new trend was recognized in the late 50's in the form at first of social psychiatry. In 1958 Doctors Redlich and Hollingshead published their now classic study "Social class and mental illness" which revealed marked differences in treatment and care of mentally ill persons in different social classes. Since then much co-operative research and teaching by Yale's faculty in medicine and the social sciences has been produced.

It is clear we are in a period of scientific and social revolution and readjustment and as Dr. Redlich points out "the challenge of the Yale School of Medicine is to produce compassionate, scientific and socially-responsible physicians". (Note the order in which he places these qualifications). This means we need a redefinition of the place in the healing profession that the majority of physicians should fill. It means the necessity of selecting and training those who are fit to fill it. The production of physicians who will combine scientific excellence in scientific training with the ability to see their patients not as cases but as human beings in a social setting is what Dr. Redlich has always wanted.

To accomplish this aim he will need to reorient curriculum. From the beginning the medical stud-

THE COVER

The management of pulmonary disease begins with clinical and physiological appraisals. The physiological test is the direct determinant for treatment.

ent will have to be taught dedication to human interest and understanding of the patient as a person. Students will need to be selected on total personality, based on determination, human interest, dedication, kindliness and curiosity as well as grades.

Dr. Redlich realizes that the educational process of students may well have to be reoriented away from facts alone towards how to reason about disease processes with the sick human being always in focus. This does not deny that a very sound scientific foundation is of the utmost importance. The sheer weight of expanding knowledge means that the medical curriculum must become either longer or more efficient and more selective. Electives will play a larger role. There must also be made provision for refreshment of graduates.

Experiments of this kind are already in progress. At Western Reserve consideration of organ systems from anatomic physiologic and molecular aspects have the advantages of confronting students with patients at an early stage. Diagnostic methods from history taking, physical examination on towards laboratory methods may come to be considered in a single course. Very important in Dr. Redlich's view is the need for regular re-evaluation of the educational process and experimentation with newer methods such as programmed instruction. He knows well that academicians like others tend to cling to vested interests.

Medical Ethics will probably receive renewed interest. Human experimentation, the meaning of death, transplantation of organs, the meaning of the legal contract between the patient and his doctor, problems involved in informed consent are some areas in which the graduate in medicine finds himself completely disoriented when he enters the field of practice. In other words we need a liaison between Medicine and Law.

Decent medical care without knowledge of the patient and his home environment is now hard to imagine. Without recognition of the doctors problem, a medical educational institution may itself suffer some ineffectiveness in the pursuit of medical excellence and at the same time produce a feeling of alienation from the Medical School and hospital amongst some community physicians. This is all fully appreciated by the new Dean who "would like to devote much time to understanding the problems which trouble community physicians and will do my best to find solutions". We wish him success in his new assignment "to make Yale University School of Medicine a place of unsurpassed excellence" by reorienting the curriculum, by introducing humanism into medicine and successfully bridging the gap between the community physicians and the School of Medicine.

L.H.N.

Science Tools: 23. The Lung Scan

Lung scanning is a simple useful clinical tool done at the bedside without any morbidity to the patient. Mishkin has performed over 30 lung scans on a selected hospital population. They first give 5 m.l. of lugols solution to block the thyroid gland from taking up I^{131} which is used in the lung scan. A total of 300 microcuries macroaggregated iodinated I^{131} serum albumin is injected intravenously with the patient supine. This gives a fairly uniform distribution of activity in normal individuals. Immediately following the injection the patient is placed in the prone position and lungs are scanned from the posterior aspect. The resultant photodot scan is then compared with a suitable chest film.

Macroaggregated iodinated I^{131} serum ablumin, is nonantigenic and when injected provides only a temporary arteriolar blockade. The blockade is temporary because the macromolecules are bulleted and eroded by the plasma and its constituents in a half-time of 5-10 hours and within 48 hours 80 per cent of the radioactivity is excreted in the urine. During the temporary blockade only a maximum of 5 per cent of the pulmonary arterioles normally numbering 227 billion may be occluded with routine dosage schedules. By this means we have a simple, accurate and thus far innocuous means for studying regional blood flow in the lungs.

The vessels which are primarily studied are the pulmonary arterioles which are end-vessels under normal circumstances supplying the respiratory bronchioles alveolar ducts and alveoli.[2,3] There is a potential collateral circulation through the bronchial arterial system which explains why infarction rarely occurs even with complete occulusion of the pulmonary artery although atelectasis will. Obviously blockade of a proximal pulmonary artery prevents normal regional perfusion of a part of the alveolar surface and will show up as a blank area in the lung scan.

Hypoxemia from whatever cause leads to pulmonary vasoconstriction so that an unventilated area will have reduced perfusion.[4] Loss of perfusion will of course lead to reduction of the alveolar pCO^2 since the usual source of CO^2, the venous blood is not present. A lowered alveolar pCO^2 through bronchoconstriction thus leads to decreased ventilation. Any condition then which can cause local pulmonary hypoxia will lead to a more or less decreased pulmonary perfusion and this will show up in the lung scan.

It is also important to consider the position of the patient during injection of the I^{131} albumin because lack of filling of the regional pulmonary vasculature not only occurs in mechanical arterial occlusion but also in physiologic pulmonary vasoconstriction secondary to reduced ventilation. In the normal person sitting up, the lower portion of the lung is perfused more than the upper. If the patient is placed in the supine position or first exercised, this slight gravitational effect is overcome and now perfusion is equal in both upper and lower lung fields.

People with significantly increased pulmonary blood flow as in left to right shunts have approximately equal perfusion of the upper and lower lung fields much like an exercising normal person. On the other hand, people with increased pulmonary venous pressure as in emphysema, mitral stenosis and left ventricular failure, may have decreased perfusion of their lower lung fields as compared to the upper lung fields because of vasoconstriction of the lower lung field vessels.

Mishkin[1] has found the lung scan useful in evaluation of pulmonary embolism regardless of whether it is large and single or small, widespread, and multiple. It has also been found useful in evaluation of regional perfusion in emphysema, cancer, atelectasis, pneumonia and after operations to relieve congenital pulmonary stenosis. In pulmonary artery occulsion the scan is accurate even though the chest x-ray may be unimpressive.

At this point it is useful to recall that the pulmonary circulation performs several functions.[2] Primarily it is thought of as a means of gas exchange. However, it also serves as a blood reservoir for the left side of the heart, as a source of nourishment to the structures of the lung beyond the terminal bronchioles, as a means of removing fluid from the alveoli to facilitate gas exchange. Finally the pulmonary circulation acts as a filtration system which prevents particulate matter from entering the systemic circulation. It is this last function which provides the basis for clinical lung scanning.

L.H.N.

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Pulmonary Blood Volume

> *". . . . . the lungs are made by Nature as if for a storehouse of blood, so that it may constantly in turn give forth blood to the heart, which, thence driven into the whole body by continued circulation may impart life and motion to everything—J. Young: Malpighi's De Pulmonibus" (1661) Proc. Royal Soc. Med., 23: 7, 1929.*

Malpighi who apparently started our interest in the pulmonary blood volume simply inflated the frog's lung and measured the amount of blood displaced from the lung. It was a qualitative method, applied by many subsequent investigators without further advancing our knowledge about the pulmonary blood volume. Quantitative measurements became possible with the advent of the heart-lung preparations at the turn of the century. What the pulmonary blood volume was in the intact animal and man required more exact methodology.

The prospect of solving this problem came in the 1920's with the introduction of the indicator-dilution technic. This method also has its limitations because it includes blood with which dye has mixed and excludes stagnant and sequestered blood. And so the method works in normals, but this is no way of predicting how the volumes and their meanings are affected either by drastic experimental conditions or by clinical disorders of the heart and lungs.

Another method to quantitatively estimate the pulmonary blood volume now available is the use of chronically implanted electromagnetic flow probes in animals around the pulmonary artery and pulmonary veins.

Traditionally the lung is pictured, as did Malpighi, as a blood depot operating to ensure an uninterrupted supply of blood to the left ventricle during acute disturbances in venous return, such as those produced by breathing, change in posture and exercise. Clearly the volume in the lungs at any instant depends on a balance between inflow and outflow as determined by the respective actions of the two ventricles. A very significant additional element is the distensibility characteristics of the pulmonary vascular tree. The pulmonary circulation operates at a low pressure, is highly distensible. It is obvious that varieties in ventilation, in total blood volume and in vasomotor activity would exert considerable influence on the volume of blood in the pulmonary vascular tree. We have yet to learn whether the distensibility characteristics of the pulmonary vasculature are affected by autonomic activity.

Even though the methods available for determining pulmonary blood volume are subject to error introduced by experimental conditions and clinical abnormalities we know that in normal subjects the pulmonary blood volume is approximately 10 per cent of the total blood volume. It is significant that with newer methods such as dilution indicator techniques and magnetic flow probes, the volume turns and to be exactly as was established long ago by direct measurements in the heart-lung preparation.

This is not of course an argument against the pursuit of more sophisticated technics in the solution of physiological phenomena, but it does remind one of a more striking story about the stroke volume. Harvey in 1628 measured the capacity of a left ventricle at post-mortem found that it was a bit over 60 m.l. and concluded that this was the stroke volume. Three and a half centuries later and with highly developed new techniques to measure the cardiac output, the stroke volume in a normal man at rest is found to be somewhat over 60 m.l.!

Aside from the lungs as a blood depot, there is the problem of its blood reservoir as the site of stretch receptors. Such receptors in the intra thoracic portion of the circulation have been postulated as devices for signalling the degree of distension of the atria and venoatrial junctions and for reflexly modifying the vasomotor behavior of the heart, the systemic resistance vessels and the kidney. Such reflexes have been described long ago by Bainbridge, McDowall, Hering and others. What mechanisms are operative during acute experimental engorgement and during chronic pulmonary congestion are not yet clear. Clarification will require more reliable technics to measure not only the pulmonary blood volume but also to determine the degree of distention of the individual cardiac chambers as well as the consecutive segments of the pulmonary circulation.

A third problem of the pulmonary blood volume is how the congested lungs perform. It has been known for a long time that lungs become stiffened by either acute or chronic engorgement. We have also appreciated that this diminished compliance of the engorged lung somehow helps to set the breathing pattern and is also involved in the genesis of dyspnea. Patients with chronic pulmonary congestion, because of their expanded pulmonary blood volume have reduced compliance, but they also have resultant fibrosis and other anatomic changes which reduce further the already lowered pulmonary compliance from engorgement. As the anatomic changes progress, they lead to obliteration of the dependent parts of the pulmonary tree. As the anatomic restriction grows one consequence may be a normal blood volume despite high pulmonary vascular pressures.

A fourth area of clinical interest in pulmonary blood volume is how to determine the partition into its various fractions, large and small fractions venous and arterial portions. The methods to determine the pulmonary arterial blood volume are still inaccurate but it can be approximated to 20-25 per cent of the total pulmonary volume.

One can see that the pulmonary blood volume has been and continues to be a subject of interest from any different points of view: the role of the lungs as a blood depot, the blood reservoir as the site of stretch receptors, the performance of the congested lung and the partition of the pulmonary blood volume. It seems likely that the next few years will see introductions of fresh technics and further clarifications of the physiological and patho-physiological roles of the pulmonary blood volume.

L.H.N.

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Thymostatin: A Thymic Hormone That Inhibits Lymphocyte Proliferation

Recently from Professor Abraham White's Laboratory at Albert Einstein College of Medicine came a report of the isolation and purification of Thymosin from calf thymus, which caused rapid lymphocyte proliferation both in vitro and in vivo.[1] In the course of their purification of Thymosin, another fraction was isolated which in contrast to the stimulating effect of Thymosin markedly inhibited both in vivo and in vitro lymphocyte proliferation. In their most recent report[2] they describe how to isolate this factor biochemically and its inhibiting effect on incorporation of labelled nucleosides in vitro in other cell types both lymphoid and non-lymphoid alike. The isolation of both Thymosin and Thymostatin, was achieved by saline extraction, ultracentrifugation, followed by a heat step, acetone precipitation, organic solvent extraction, gel filtration and ion exchange chromatography.

There have been a number of investigators who reported the isolation of thymic tissue preparations that inhibited cellular metabolism both in vivo and in vitro. Several of these products have been characterized clinically as histones or basic peptides.[2] The effect of these substances on incorporation of labelled precursors into DNA, RNA and proteins are well documented. The difficulty has been however that the mechanism of their action appeared to be complex and not completely understood. The cellular inhibitions of these preparations include several metabolic functions ranging from transport and oxidative phosphorylation to a possible role in the transcription and control of genetic information.

In addition certain products exhibited an antibiotic activity. Thus Dubos and Hirsch[3] reported the isolation of a basic water soluble peptide from calf thymus that under specific conditions in vitro possessed potent anti-mycobacterial activity. Then there is the work of Szent-Györgi on retine,[4] a methylglyoxyl derivative, that was cytotoxic to various cancer cells in vitro and also inhibited tumor growth in vivo.

Most recently in a report of a conference it was stated that Hinshaw and Jolly[5] isolated lysine and arginine-rich peptides which when injected into mice inhibited the growth of transplanted sarcoma-180 or C-6 myeloma tumors. Also Holubeck[6] has prepared from nuclei of Ehrlich ascites cells arginine and lysine-rich histones. The arginine-rich histone suppressed the incorporation of labelled uridine or Thymidine into Ehrlich ascites cells, whereas the lysine-rich histone stimulated the in vitro incorporation of uridine and Thymidine by the same Ehrlich ascites cells.

On the basis of chemical composition and biochemical action in vitro, Thymostatin does not appear to be identical with any of the previously described inhibitory substances from thymic tissue. The amino acid composition of Thymostatin does not resemble that of a histone and its biochemical effects are more restricted since it inhibits only the incorporation of nucleosides under the conditions of the assay used. The thymic peptide of Dubos and Hirsch is acetone insoluble and does not contain carbohydrate. Szent-Györgi's retine is very unstable, volatile and extractable in chloroform. Thymostatin is stable not volatile and is not soluble in chloroform. The last but not least significant point of difference between Thymostatin and the other substances, is that effects of Thymostatin can be removed by washing the cells. Thymostatin effects in other words are readily reversible.

The biological activity of Thymosin and Thymostatin is such that the two substances, having opposite effects, can be titrated against each other. Based on protein concentration, Thymostatin is significantly more potent than Thymosin in the present state of purity of each. In order to prevent lymphocyte proliferation in mesenteric lymph nodes, approximately ten times as much Thymosin is needed in the incubation medium.

The biochemist looks at this great discovery and thinks Thymostatin should prove to be useful for elucidation of processes regulating the synthesis of macromolecules, because while it inhibits precursor incorporation of DNA and RNA it does not prevent protein synthesis. It is further warranted to postulate that Thymosin and Thymostatin are humoral agents that have a role in the homeostatic regulation of lymphoid tissue structure and function.

The clinician would like to leap forward a bit. Thymostatin also inhibits other cell types such as rabbit thymocytes, rat lymphosarcoma cells and He La cells in addition to mesenteric lymph node cells. We would like to see what Thymostatin does to lymphocytic leukemia, to lymphosarcoma to lupus erythematosus. But we must wait since the researchers tell us "other possible effects of this preparation in vivo and its relationship to Thymosin and other cellular control mechanisms are presently under investigation."

L.H.N.

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Acute Myocardial Infarction And Hyperglycemia

Hyperglycemia is often associated with acute myocardial infarction. This phenomenon, long known, is generally accepted as a common occurrence since Cruikshank's report in 1931[1] and many confirmatory reports since.[2] What its possible significance is and what its relationship is to diabetes mellitus forms the basis of a recent report by Datey and Nanda[3] on 167 patients with acute myocardial infarction that were carefully studied for disturbed carbohydrate metabolism soon after admission to the hospital and periodically thereafter. The usual criteria for existence of normal and diabetic responses were followed by determining urinary glucose, blood glucose and glucose tolerance curves. The authors were careful not to confuse the basic problem by eliminating from the study those patients that were known to have diabetes, or a family history of diabetes or were receiving thiazide diuretics.

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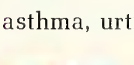

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Several facts were clearly substantiated. In a high proportion of cases of acute myocardial infarction there follows an immediate disturbance of carbohydrate metabolism. Sixty-five per cent of Datey and Panda's cases showed initial hyperglycemia which persisted for one week. At the end of a month it was found in twenty-nine per cent. Of fifty-seven cases tested after one to two years the incidence of hyperglycemia had declined from 70 to 31.5 per cent. Of these latter 17.5 per cent had abnormal glucose tolerance curves but no clinical diabetes, while 14 per cent developed clinical diabetes. All normal controls remained normoglycemic.

The study further reveals that fasting blood sugar levels except in a minority did not demonstrate the abnormality in carbohydrate metabolism which however became apparent only by post-prandial tests and glucose tolerance tests. As was to be expected, the incidence of hyperglycemia was higher in persons over fifty years of age. Furthermore the extent of cardiac damage seemed to play no role nor did obesity in the few patients found in the series.

Glucose tolerance is known to decrease with advancing age especially in subjects over fifty.[4] The higher incidence of disturbed carbohydrate metabolism in Datey and Panda's cases may partly reflect the effect of age on glucose tolerance. Whether this is a physiologic manifestation of the aging process or whether it denotes diabetes mellitus in the accepted sense has not yet been finally established. The relation of hyperglycemia to diabetes is quite variable in reports in the literature. In general however abnormal curves did not all remain so. They declined from seventy-three to forty-three per cent after six months and after two to three years twenty-seven per cent still had abnormal glucose tolerance curves but not clinical diabetes.

The normal patients remained normal even after age fifty, not one developing diabetes. Of the abnormal ones thirty-eight per cent showed transitory hyperglycemia which had no relation to diabetes mellitus. This means that one must not be too quick to make a diagnosis of diabetes for at least a month after an acute myocardial infarction. Even after this period, glucose tolerance curves should be studied every few months in the initial hyperglycemic patient before labelling a case as having diabetes mellitus. However fourteen per cent of all patients had latent diabetes unmasked during acute myocardial infarction by exhibiting diabetic glucose tolerance curves.

There have been various mechanisms postulated to account for the high incidence of hyperglycemia after acute myocardial infarction. One considers the possibility of coexisting arteriosclerotic degeneration of the pancreas. Another holds that chest pain stress is sufficient to increase adrenocortical production. Recently Vallance-Owen and Ashton[5] found increased insulin antagonism that persisted for as much as three months after the acute attack. This finding is consistent with the idea of a transient increase in adrenocortical function.

The lesson to the physician who treats a patient for acute myocardial infarction especially if the patient is over fifty years of age is clear. Any patient with acute myocardial infarction should have a post-prandial blood sugar test and if it proves to be above normal, the patient should from then on have life time supervision. Such a patient should take the usual dietary precautions for protection against the development of active diabetes. The physician will certainly recommend avoidance of sweets in any form and if the patient is overweight, he should be urged to limit the total food consumption as an important measure against development of overt diabetes.

Equally important prophylactically is the need for post-prandial tests of the urine and blood sugar determinations periodically and especially at any time of stressful situations. There is of course no cause for pessimism if a patient is found to have hyperglycemia after acute myocardial infarction, since the majority of such patients actually are not diabetic. At the same time such a finding should alert the physician and the patient to the need for precautions.

L.H.N.

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Artificial Materials In Surgery: In Cardiovascular Disease

The cardiovascular system is the object of the newest, very successful and most dramatic invasion by the surgical implantor of artificial materials, and much has been learned concerning the fate of arterial prostheses. Many basic biological observations have yet to be made however before exact specifications of cardiovascular prostheses can be established.

Many implants consist of two or more types of materials. For example valve implants consist of a metallic cage, a solid plastic wall and a sewing ring of textile. The fate of solid metal implants would be related to the chemistry at the implant site while healing is determined primarily by physical porosity of the arterial wall. Then there are the complications in cardiovascular implants such as fibrin deposits which must be avoided since they interfere with healing and contribute to possible embolus formation. [1, 1a]

In the heart, implantation of cardiac valves, filling of mural or septal defects and implantation of permanent pacemakers are now regularly practiced in many centers in this country. Prosthetic devices to assume the pumping function of the heart will come but are now in the developmental stage.

The first artificial valve was the Hufnagel valve placed in the descending aorta for cases of frank regurgitation. It was a complete valve in a lucite housing, around which the aortic ends fit tightly. The next one was the Starr-Edwards valve, a metallic ball retaining cage which is made of a cobalt-chromium-molybdenum alloy. It is very hard, resistant to corrosion and mechanical wear and prevents fibrin deposition when in contact with blood. Inside the cage is a solid ball of silicone and around the base of the retaining cage is a cuff of textile of knitted polytetra fluoroethylene. The textile is used for direct suture to the annulus of the aortic ring after resection of the aortic valve.

Some of these valves are still functioning after five years but there is still a rate of embolism of ten to fifteen per cent and there is some residual systolic gradient especially in small diameter valve rings. There are other problems such as decreased survival time of red cells. Clearly refinements in hydraulic design and method of fixation to allow optimal healing without embolism are still necessary. Experience with pliable valve leaflets of textiles has been disappointing because of a high rate of embolism. Aortic valve homografts develop a high incidence of stenosis and also occasionally rupture and this makes them unacceptable.

Ball valve prothesis have been used also in the mitral valve region but have been reserved only when simple valvulotomy by the conservative approach in mitral stenosis is ineffective, especially when much regurgitation is present. However regurgitant lesions can be treated by annuloplasty or by advancement, which should first be tried and only if inoperative, is the ball valve prosthesis considered. Pulmonary stenosis usually lends itself well to valvulotomy.

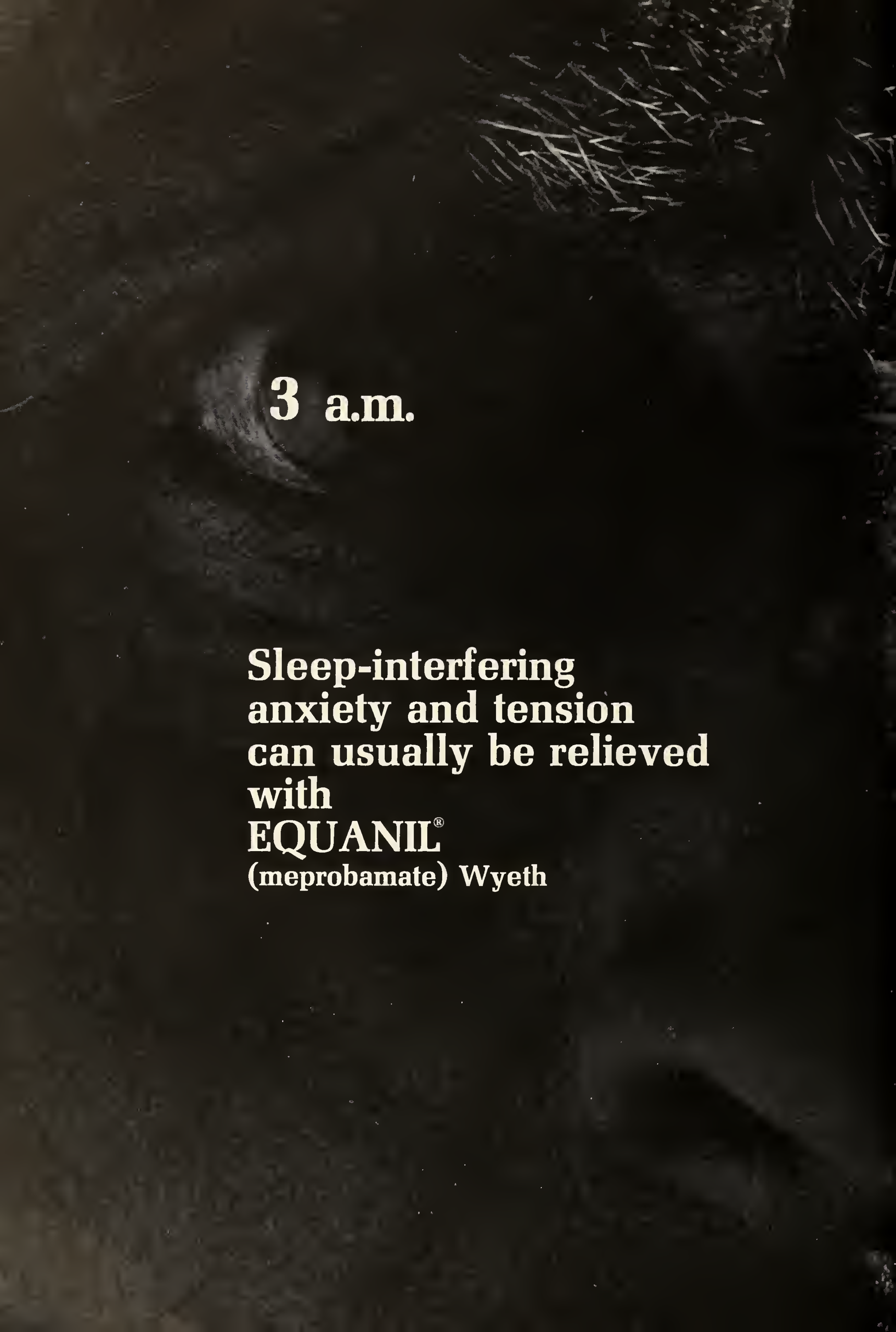
Replacement of mural and septal defects of the heart with artificial materials has been practical for a decade. Compressed ivalon was first used, then knitted teflon products and more recently the weave-knit and other dacron patch materials which are both pliable and suturable. The complications are few, the healing line is stable. There is an elaboration of a pannus which grows over the textile for a distance of one to two cm. If the prosthesis required is over four cm. then complications of healing do occur. In such situations autogenous pericardium has been used for successful replacement of mural and septal defects in the heart.[2]

The first practical use of pacing the heart electrically was developed in conjunction with open heart surgery a decade ago in order to compensate for conduction defects occurring in some patients following closure of ventricular septal defects. The first method was to suture a stainless steel electrode to the myocardium and its wire then led out through the anterior chest wall and connected with an external pacemaker. The heart can also be paced via an insulated intraventricular electrode inserted through the jugular vein in the neck. Thereafter completely implantable pacemaker units were rapidly developed.

Most of them employ electrodes which are sutured directly to the apex of the ventricular myocardium during thoracotomy. However a better placement of the electrode for pacing the heart would be midway in the anterior septum.[3] The insulated electrodes are looped in the mediastinum and drawn either subcutaneously or through a subcostal tunnel to connect with a subcutaneous or subfacial pocket in the anterior abdominal wall. The pocket serves as a repository for a transistorized battery energizer pacemaker. Most pacemaker pulse generators are coated with silicone to insulate the pacemaker elements from contact with body tissue. Silicone also insulates the electrodes up to the point of contact with the myocardium. An ideal to pursue is some arrangement that would not require a thoracotomy.

The healing of pacemaker implants appears to be by simple encapsulation by fibrous tissue of the material that comes into contact with the tissues. The silicone, once a fibrous capsule forms around it, is well tolerated. One of the early problems with pacemaker implantation was the liability of the electrodes to break. Some of the physical factors contributing to the practice were overcome by avoiding electrode flexion at a fixed point and employing generous loops of electrodes in the chest as well as around the pulse generator. Another precaution was to avoid angulation of the wires as they are drawn through an intercostal space into the subcutaneous region. Another improvement was the development of helical spring electrodes. This has significantly lengthened the expected mechanical longevity of the electrode.

Pulse generator units now have an estimated life of five years, but longer periods of observation will be required to confirm this figure. At present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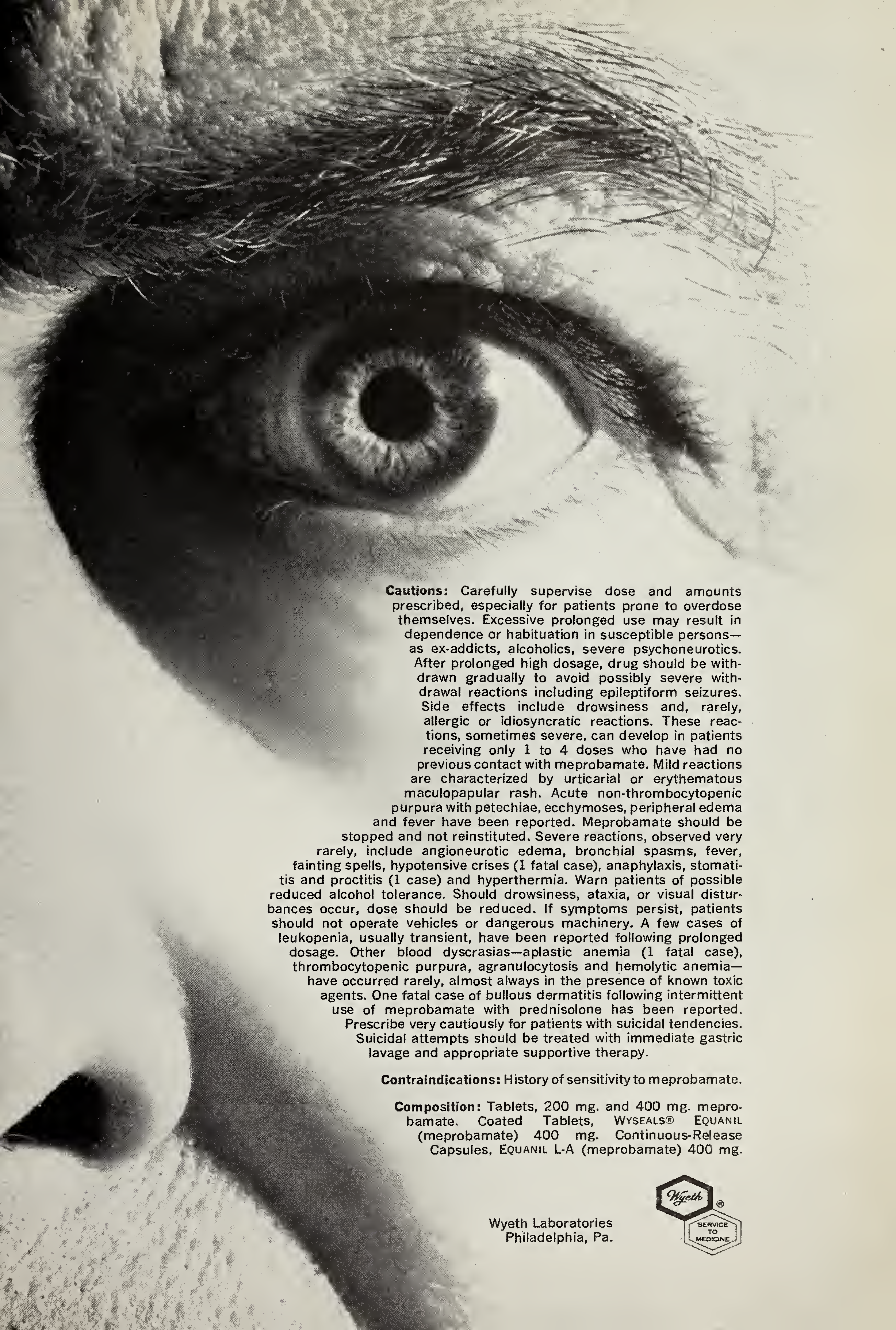

Cautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use may result in dependence or habituation in susceptible persons—as ex-addicts, alcoholics, severe psychoneurotics. After prolonged high dosage, drug should be withdrawn gradually to avoid possibly severe withdrawal reactions including epileptiform seizures. Side effects include drowsiness and, rarely, allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute non-thrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. Meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Warn patients of possible reduced alcohol tolerance. Should drowsiness, ataxia, or visual disturbances occur, dose should be reduced. If symptoms persist, patients should not operate vehicles or dangerous machinery. A few cases of leukopenia, usually transient, have been reported following prolonged dosage. Other blood dyscrasias—aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia—have occurred rarely, almost always in the presence of known toxic agents. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. Prescribe very cautiously for patients with suicidal tendencies. Suicidal attempts should be treated with immediate gastric lavage and appropriate supportive therapy.

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L.H.N.

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Propranolol In Cardiac Arrhythmias

We have known for a long time that the autonomic innervation of the heart plays a major role in its efficiency. The heart rate is a result of a fine balance between inhibitory and accelerating influences upon the pacemaker. Conduction through atria is slowed by acetylcholine and increased by norepinephrine liberated at endings in the atrial musculature. Conduction through the A.V. node is also finely balanced, being slowed by vagal and accelerated by sympathetic influences. The ventricular masculature in man and other mammals receives and responds only to sympathetic neurohormones, epinephrine and noreprinephrine.

A major step forward in our understanding of the role of the nervous system in cardiac function came when it was recognized that arrhythmias are intimately related to the action of autonomic neurohormones. Atrial tachycardia and ventricular tachycardia were dependent in part upon the action of the catecholamines. Animals deprived of their sympathetic control of the heart did not develop the regular tachycardias in the presence of chloroform, benzol and other fat solvents. To produce this deprivation, required section of the stellate ganglia and adrenalectomy.[1]

With the introduction of the beta-adrenergic blocking agent pronethalol and the more recent availability of its analogue propranolol, it has been possible to confirm the experimental work on the role of the sympathetics in cardiac arrhythmias. For if the results observed in animals are applicable to the clinical situation then, paroxysmal atrial tachycardia and paroxysmal nodal and ventricular tachycardia should be abolished by blocking the sympathetic endings in the heart. One should observe slowing of the heart rate and slowing of conduction through the A.V. node also by abolishing the sympathetic part of the control. Once the blocking agents became available, it was not surprising that their use should have been extended in treating certain cardiac arrhythmias, in view of the known role of the beta receptors (sympathetics) in their production.

Luria, Adelson and Miller[2] have described as have other before them the acute and chronic effects, of propranolol in the treatment of cardiac arrhythmias. This study is based on observations on twenty-nine patients. In atrial fibrillation the ventricular rate was slowed by propranolol. In seven the ventricular rate couldn't be controlled by large doses of digitalis. Five of them had received propranolol over long periods of time, but as might have been anticipated two patients developed congestive heart failure in the process of controlling the heart rate, because evidently they were deprived by the beta-adrenergic blocker of that element of cardiac reserve—the inotropic effect, upon which the heart often defends for its efficiency.

Both supaventricular tachycardia nodal and ventricular trachycardia were readily abolished by propranolol regardless of the precipitating cause.[3,4,5] The sinus slowing, A.V. block and depressed ventricular automaticity produced by propranolol nicely delineates what happens to a heart that is deprived of its sympathetic control.

From the clinical standpoint troublesome sinus tachycardia should readily be controlled by propranolol as happened in three of Luria's patients. Similarly propranolol should produce dramatic slowing of the ventricular rate in atrial fibrillation by freeing the vagus at the A.V. node to exercise its full inhibitory effect. This happened in Luria's patients also.

There are limitations upon the use of a beta-adrenergic blocker. Some patients with cardiac arrhythmias are often seriously ill especially those following digitalis overdosage and frequently manifest concomitant congestive failure or are on the verge of congestive failure, being kept out of this state by the reserve obtained from the action of the beta receptors. In this situation an anti-arrhythmic drug without adverse effect on cardiac contractility would be desirable. Unfortunately propranolol by virtue of its beta-adrenergic blocking activity may impair myocardial function. Actually overt congestive failure developed in two patients and significant hypotension occurred soon after intravenous infusion of propranolol in three patients. Those who use propranolol in cardiac arrhythmias must realize therefore that careful clinical observation of the patient is mandatory since the drug may have an adverse effect on individuals with limited myocardial reserve.

Realizing that there are definite limitations for the use of propranolol it does have clinical application in certain selected disturbances of cardiac rhythm. It effectively slows the ventricular response in chronic or supraventricular arrhythmias not adequately responsive to digitalis glycosides. In addition it is a useful agent in the prevention of paroxysmal tachycardia arising in any point of the mycardium, paroxysms which are predictably induced by exogenous stimuli.

The introduction of beta-adrenergic blockers as well as alpha-adrenergic blockers is the second phase in the development of our knowledge of the role of the autonomic system in cardiac function. In the first, a basic understanding of the physiology of the heart under conditions varying the action of the two regulators of heart rate and function was elucidated. The development of drugs blocking the effects has given impetus to the pharmacologic study of the roles of the autonomics in cardiovascular function and has led to clinical application in a variety of disorders of cardiac rhythm and cardiac efficiency.

L.H.N.

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Exercise In Heart Disease (1). Physiology Of Physical Fitness

We know that inactivity reduces the capacity of the body to meet extraordinary demands and even to perform properly ordinary daily activity. We also know that a well-planned program of physical training—termed conditioning—improves the capacity for exertion. One could from these physiological benefits of conditioning take a position that it is good for all people to strive to be in the pink of condition especially since life is full of unexpected periods requiring extraordinary exertion that result from physical and emotional stresses. In short that a training program has a good purpose and one that should be pursued.

Two questions present themselves in regard to physical fitness in coronary heart disease. One is how does exercise improve the mechanical efficiency of muscles and heart. The other and equally important one is whether physical conditioning plays any role in arresting the factors which lead to atherosclerosis and therefore could serve to promote longer life.

It is definitely established that exercise can improve the mechanical efficiency with which muscular performance is carried out. We know that there results a reduction in oxygen requirements that the muscle needs to perform a given amount of work. This is accomplished by an improved capacity of the body to buffer the lactic acid produced by the muscles during exercise. There is a greater blood hemoglobin content. Then there is a better heat disposal mechanism and many others.

All of these delay the onset of development of oxygen debt during exercise, lessen the oxygen need for a given amount of work and for a given rate of muscular work. Stated another way there is improved efficiency with which energy is used in exercise and this accounts for the improvement in physical fitness. There is also improvement in a persons motivation to develop his performance. All these lead to certain general benefits in many tissues and organs of the body.

A person who engages in a physical fitness program finds improved capabilities for relaxation. He finds he can endure more fatigue with pleasure. But also he augments his muscular tone. He can do more and recover from exertion more rapidly. He carries out his exertion with some relaxation and with less extraneous waste motion. Hopefully he will lose some of his fat deposits.

His respiratory system also improves. He ventilates less for a given exercise and for a given level of oxygen need. His vital capacity increases and so does his maximum breathing capacity. For any given work load, respiratory rate is lower and therefore breathlessness is delayed. The deeper and slower breathing of course lessens the wastage from the pulmonary dead space.

In the state of physical fitness we find that the liver releases glucose more readily to the blood and also metabolizes better the lactic acid produced during exercise. In consequence blood lactate rises less and the respiratory center is not driven too easily to accelerate breathing. In the blood we find an increase in volume, in number of red blood cells, in the amount of hemoglobin and in its oxygen carrying capacity, all calculated to improve oxygen delivery to exercising muscles and improve efficiency.

The benefits of physical fitness to the circulatory system are equally great. If we compare a trained with an untrained person we find that training slows the heart rate at rest and for each level of exercise as compared to the untrained person. The trained person has a larger stroke volume because the diastolic residue declines and this is an important element in the increased cardiac output. This ensures that the oxygen cost to the heart for a given work load is reduced exactly as it is in skeletal muscle. It is recognized that the oxygen requirements for a given work load is a function of the heart rate and the chamber size. Training reduces the heart rate and the size of the heart required to meet any given work load.

This means as mentioned above that the heart rate is slower both at rest and at any given work load in a trained than in an untrained person. Furthermore the heart does not increase as much in size in the trained as in the untrained person, when a given work load is imposed, even though the resting heart size is greater in the trained than in the untrained person. The trained person has a somewhat greater heart muscle mass and this helps to supply the energy needed by the heart. If the person were untrained this energy would come from increased dilatation and accelerated heart rate, both of which greatly increase the oxygen burden upon the heart. Obviously if the oxygen cost per given amount of work of the heart is raised it can only come from increased demand upon the coronary circulation.

In the trained person the systemic blood pressure during ejection is lower at rest and at any given degree of exercise. This is the result of a reduction in peripheral resistance. Obviously the lesser oxygen requirement of the heart of a trained subject as compared with an untrained one, means the need for lower coronary flow rates both at rest and during any level of bodily exertion. Since the heart rate is slower at any given level of exercise in the trained person, the heart spends more of its time during diastole when coronary flow is unimpeded by the ejection phase. It is clear why a heart of a trained person is more effiecient: it operates at a lower systemic pressure, with increased stroke volume and slower heart rate, and its metabolic machine is improved, thereby enhancing its contractility. All of these factors reduce oxygen requirements for a given amount of work and reduce coronary flow rates.

It is also possible that the body learns better how to distribute blood form inactive muscles, skin, splanchnic areas and kidney to the active muscles, heart and brain where the oxygen is being used. Such a mechanism can also reduce total oxygen needs during exercise and therefore the need for coronary blood flow in a trained person for a given amount of exercise.

We can see that in heart disease generally and in ischemic heart patients in particular, training can lead to a decline in the heart's requirement for oxygen and for coronary flow. If this be true then training holds the promise that it could be valuable in ischemic heart disease and that physical fitness is good for such patients. Besides this there is considerable evidence that an exercise program has another advantage, that of accelerating the growth of coronary vascular collaterals particularly when the coronary arteries are insufficient to allow blood flow for ordinary needs let alone that which would be required for extraordinary states of physical and emotional efforts. Finally and equally important is the reassurance that a patient receives from a training program, that the physician does not regard him as an invalid unfit for work or a productive life.

In considering a training program both physician and patient must play their respective roles. The physician must carefully evaluate his patient to determine what part of his incapacity is due to disease and what part is due to physical unfitness. A probe of mild training under supervision can help the physician to determine the rate at which physical training shall be pursued without undue hazard to the patient.

The patient also needs to be informed of the signs and symptoms which indicate that he is doing too much or is accelerating his training schedule too rapidly. He must be told to avoid *exhaustion,* chest discomfort and shortness of breath. These signs and symptoms if brought on by exertion must not be allowed to persist too long nor should they increase after the exercise is stopped. "Walking through angina" should probably not be allowed unless there is clear evidence that the patient has himself previously done so and improved by continuing the effort. Otherwise physical exertion should not be carried out to near capacity because of the ever present fear of ventricular fibrillation following the occurrence of ventricular premature systoles.

L.H.N.

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Prevention Of Experimental Atherosclerosis By Peroxidase

Atherogenesis in man and experimental animals appears to be associated with an elevation of serum cholesterol. The mechanism relating these two con-

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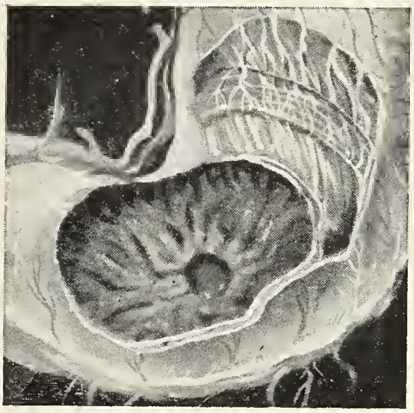

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ditions may be somewhat as follows: the non diseased arterial wall exhibits a certain permeability to cholesterol that allows a balance between the influx and removal of this lipid so that no accumulation occurs. For accumulations to occur two mechanisms might be postulated: the barrier to cholesterol entry could be damaged by arterial injury allowing excessive cholesterol accumulation even when the serum cholesterol is normal. Such a situation occurs experimentally when normal aortas are damaged by cyanide, mechanical injury, by scraping or freezing, certain chemical poisons and anoxia.[1] A second condition would be when blood cholesterol levels are elevated. In this case the influx of cholesterol would increase so much that the removal mechanism lags behind so that arterial cholesterol deposits develop even when the arterial barrier to cholesterol is normal.

Whether the arterial barrier to cholesterol entry is broken down or whether, there is excessive circulating cholesterol, once it penetrates the aortic wall it indicates biochemical ultra-structural and histo-pathologic alterations. The morphological end results are degeneration of the aortic elastic fibers and smooth muscle with an increased deposition of collagen. Thickened fibrotic areas mingle with sudanophilic fat to form gross internal placques. The exact relations between these processes are unknown but in general increased aortic and mucopolysaccharides are observed in reactions to injury and neutral mucopolysaccharides predominate in the stabilized situation as observed in the repaired state.

If we knew how to reduce the serum cholesterol levels to normal we could prevent atherosclerosis that results from hypercholesterolemia. Several approaches to the solution of this problem present themselves for consideration. One is the time honored method of greatly reducing the cholesterol intake from food. Another has been the attempt to increase oxidations of cholesterol and other lipids by thyroxin and estrogen. A third has been to attempt to reduce cholesterol biosynthesis in the liver. It is to the solution of the last that Caravaca et al have just contributed an important enzyme, hepatocatalase peroxidase (HCP).[2]

These investigators have just isolated a sub unit of HCP whose peroxidatic activity is 500 times higher than that of the intact catalase molecule. This sub unit inhibits cholesterol biosynthesis from acetate and mevalonic acid, (the precursors of cholesterol) by homogenates of rat livers. HCP has another important effect; it catalizes aerobic oxidations of a number of hydrogen donors, all of which play a significant role in lipid metabolism. These are the oxidations which are also stimulated by thyroxin and estrogens. We therefore have an interesting model for a homeostatic control mechanism of cholesterol metabolism, its rate of synthesis as controlled by HCP and it's rate of oxidation as regulated by HCP, thyroxin and estrogen. What then would HCP do in vivo?

Caravaca and his group administered HCP to normal rabbits with hypercholesterolemia and atherosclerosis induced by feeding the animals a normal diet plus 0.8 grams of cholesterol daily for fifteen weeks. Half of the animals received 80 units of HCP dissolved in 1 ml. of isotonic saline. The enzyme treated animals showed a significant decrease of tissue cholesterol, serum triglycerides, cholesterol, phospholipids and B lipoproteins as well as a decline in serum cholesterol levels.

As good scientists they looked for signs of toxicity and allergic reactions throughout the experimental period. The HCP was well tolerated by rabbits, rats and guinea pigs receiving as much as 1000 units/kg. daily for a period of over two months. Neither SGOT, alkaline phosphatase, BUN, crea tine or glucose was affected by the enzyme since the values remained within normal limits. The next question was whether any reacting antibodies appeared in the serum of rabbits to HCP, and so immunological studies made at various stages of treatment with gel diffusion, auto radiographic techniques disclosed no evidence of HCP reacting antibodies.

The conclusion was inescapable that HCP treatment of cholesterol fed rabbits protected them from aortic and medial injury and its consequences to a significant degree. To be sure under the experimental conditions of massive feeding, the enzyme did not completely prevent cholesterol damage. It did however lower serum cholesterol by preventing cholesterol synthesis and facilitating the oxidation of much of the excess derived from diet.

We have then in HCP an enzyme that participates in the homeostatic control of lipid and cholestrol metabolism with a great potential to control atherosclerosis that is due to hypercholesterolemia. If Caravaca's results are confirmed we will be in possession of an agent that can regulate blood cholesterol as insulin regulates blood sugar.

L.H.N.

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Seborrheic Dermatitis	18	442	426
Atopic Dermatitis	24	460	426
Psoriasis	36	1,699	1,510
Neurodermatitis	18	351	324
Total	144	4,174	3,808

*Complete bibliography on request.

†Expressed by the authors as excellent, very good, good, complete remission of inflammation, etc.

PRESCRIBING INFORMATION
For initiation of therapy: Cream 0.025%, 5 and 15 Gm. tubes, 425 Gm. jars; *for emollient effect:* Ointment 0.025%, 15 Gm. tubes; *for maintenance therapy:* Cream 0.01%, 15 and 45 Gm. tubes, 120 Gm. jars; *for intertriginous or hairy sites:* Solution 0.01%, 20 cc. and 60 cc. plastic squeeze bottles; *for infected inflammatory dermatoses:* Neo-Synalar® Cream (0.025% fluocinolone acetonide, neomycin sulfate, equivalent to 0.35% neomycin base), 5 and 15 Gm. tubes.
CONTRAINDICATIONS: Tuberculous, fungal, and most viral lesions of the skin, (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. PRECAUTIONS: Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Prolonged use of any antibiotic may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy should be instituted. When severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. SIDE EFFECTS: Side effects are not ordinarily encountered with topically applied corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. The neomycin in Neo-Synalar Cream rarely produces allergic reactions.

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MEDICAL NEWS

Family Communications And Disturbed Adolescents

Teenagers are continually complaining that their parents don't understand them.

At Chicago's Michael Reese Hospital, a group of psychiatrists listened more closely, however, when they heard this complaint again and again from young people undergoing psychiatric treatment.

Based on subsequent studies of 20 families, the investigators conclude that there may be something to youngsters' complaints.

Good communication within the family, they said, seems to be a major factor in helping the teenager adjust to his problems and in meeting the goals his parents set for him. Conversely, it is poor communication that seems to increase the anxieties of disturbed adolescents. Carried to extremes, these breakdowns in family communications may result in the need for psychiatric help.

A report on these findings appears in a current American Medical Association publication, the Archives of General Psychiatry (December).

In extensive interviews with the authors, children from 10 "normal" families expressed relatively little anxiety about communicating with their parents, brothers and sisters. Their parents seemed to be good communicators — persons who could make their wishes clearly understood to their children.

The result, in these families free of major psychological disturbance, was a closeness between what parents expected of children and what the children understood to be their parents' wishes.

The adolescent in these so-called "normal" families had relatively little trouble in explaining how he felt about himself—his self-image—to his parents.

The situation was markedly different in "disturbed" families. One 17-year-old high school senior was hospitalized because of an acute withdrawal from social life and failure in his school work.

He described his mother as an "overwhelming" person, and insisted that he was unable to follow her demanding expectations.

A younger brother left home and enlisted in the armed forces to "escape the control" of the mother, he said.

Frequently, the mother of disturbed children explained unusual behavior of their children as a rebellion against them and their ideals. There is considerable evidence, however, that these children weren't rebelling at all, but simply didn't understand the mother's expectations, the authors said.

"It was clear that all members of the normal families understood what society expected of them, and generally they tried to live up to this expectation. When they didn't they were well aware of the degrees of this deviation.

In disturbed families, a significant finding was that the mothers knew very well what society expected. "However, this awareness was not as consistent as was that in normal families, and was considerably decreased in stressful situations.

"It was as if these mothers had memorized 'the correct answer' but could not keep to this line of reasoning for consistent periods."

Disturbed children recognized that they were not living up to social norms, the authors said. "In general, we felt that the mothers of disturbed adolescents were excessively critical of their children's failures and tended to undermine their successes by means of confusing messages."

These mothers "tended to emphasize mastery of certain tasks which, once mastered by the children, was immediately minimized."

In contrast, mothers in the normal families used a more appropriate method of stimulating initiative in their children, and showed a flexible approach to problems, one without the extreme, unrealistic demands made by the mothers of disturbed children."

The children in the healthy families showed positive feelings toward their accomplishments and successes, in contrast to the children in the disturbed families who were either grandiose or excessively self-depreciating, the authors said.

The authors are David Marcus, M.D., and Daniel Offer, M.D., of Michael Reese Hospital, Chicago; Sydney Blatt, Ph.D., Department of Psychiatry, Yale University, New Haven, Conn.; and Gerald Gratch, Ph.D., Department of Psychology, University of Houston, Houston, Texas.

Pulmonary Disease Issue

Frank D. Gray, Jr., M.D., *Guest Editor*

Introduction

■ Over 20 years ago Dickinson Richards, Andre Cournand, and the late Eleanor DeForest Baldwin combined their physiological genius, masterful teaching and infectious enthusiasm to produce a force that influenced many medical students to enter the field of clinical chest disease which was considered dull at that time, but just as important were their efforts to bring intricate laboratory studies directly to bear on the practical clinical problems of emphysema, cor pulmonale, and a host of other chronic chest diseases. As a result of their writing and teaching, medical centers began to establish cardiopulmonary laboratories and special services for the care of the patient with disabling pulmonary disease. It was, however, a highly specialized kind of practice.

Now the time is past when the family physician can shift responsibility for the management of complicated respiratory insufficiency to the specialist. When Richards, Cournand, and Baldwin started their program, the more severe forms of pulmonary disease led to death in a discouragingly short period of time, and responsibility for the supervision of the complex procedures necessary to maintain minimal function was assumed by teams, like theirs, of clinical physiologists in the hospital. To-day, patients suffering from serious respiratory diseases may be discharged from the hospital with permanent tracheostomies and mechanical ventilators, to carry on useful existence for many years; consequently the family physician is faced with the necessity of understanding in detail the physiological impairments and their necessary corrections.

The continuing medical knowledge that physicians use as a tool to treat ill patients derives from two sources. In the first place, every physician has the basic knowledge that comes from his medical school and hospital training cultivated by subsequent experience and sharpened by continual review. Secondly, owing to the perpetual flux of clinical thinking, the physician must bolster his basic knowledge by having recourse to medical literature and post-graduate training. The first category of clinical knowledge, that obtained from training and experience, was at one time the dominant feature of practice, but in to-day's rapidly changing medical environment, it is becoming less important as the second category becomes dominant.

In all sub-specialties of medicine progress is moving so fast and concepts changing so rapidly that the medical student is no longer given the basic tools of his trade, but rather the school attempts to cultivate the intellectual equipment he needs to acquire those tools. In the specific sub-specialty of chest diseases, the medical student, and even the house officer completing his service, has only a scant background of training in current pulmonary physiological thinking. Some students and house officers have taken it upon themselves to become proficient in this field, others have become proficient in other sub-specialty fields, but very few have embraced all fields and most have devoted their training period to developing their general learning ability. The result is that the physician entering practice today has a great part of his education before him. Since he is faced with the necessity of managing complex physiological medical problems, it is necessary that the teaching resources, the medical school and hospital, which formerly provided this information to the under-graduate or house officer, now assume the responsibility of providing specialized on-the-job training for the practicing physician.

With this purpose in mind, the Editor of Connecticut Medicine has invited the members of the Yale-New Haven Medical Center's Chest Section to prepare a selected group of reports on some of the newer chest disease topics. We have made no attempt to survey the entire field. Instead, we have chosen selected areas of clinical chest medicine, pathology, and physiology which, if understood in detail, would permit the physician to meet his responsibilities for almost any kind of chest problem he might encounter in his practice.

Some of these subjects are difficult to understand. This is true for the physician who has long been in practice as well as for the student recently graduated, for neither has had formal training in these newer concepts. Modern medicine is, however, inherently complex and each of us must attain for himself some kind of resolution of this difficulty. We hope that some will find help from our reports in this issue of Connecticut Medicine.

Ventilation-Perfusion Ratios In Cardiopulmonary Diseases

Frank D. Gray, Jr., M.D.

■ Knowledge of respiratory gas exchange and the bellows action of the lung is very old, but practical means of assessing lung function were almost nonexistent, except for vital capacity measurements, until shortly before the second World War when the spirometer became a frequently used instrument for the study of the clinical physiology of the lung. Since then a number of highly refined mechanical devices have been developed to estimate blood gas tensions, pulmonary compliance, and diffusing capacity to mention just a few. These are methods of expressing information which has long been part of our physiological concepts of lung function.

Two new concepts originating in their expressed forms after the second World War have attained sufficient importance to require that clinicians understand them clearly. The first of these concepts is embodied in the oxygen-carbon dioxide diagram. It was demonstrated by Fenn, Rahn, and Otis[1] in 1946 as a graphic representation of respiratory gas exchange. This concept was further refined by Riley and Cournand[2] in 1949 when they proposed the "ideal" alveolar air concept which identifies the theoretical alveolar gas tensions which would exist in the presence of perfect gas exchange. The second major concept, the ventilation-perfusion ratio of the lung, derives much of its validity from the first concept, and was originally expressed by Rahn[3] and Riley and Cournand[2] in 1949. For optimal exchange of oxygen and carbon dioxide, the lung must receive air (ventilation) and blood (perfusion) in a very precise ratio to one another.

The oxygen-carbon dioxide diagram is a graphic way of expressing the physical-chemical events leading to the alveolar-capillary respiratory gas equilibrium. The ventilation-perfusion ratio concept identifies the two main variables on which gas exchange depends in terms of a single quotient.

A major purpose of respiration is to meet the metabolic needs of the body for oxygen and carbon dioxide exchange. This exchange is expressed as a ratio (or quotient) of carbon dioxide produced to oxygen used, and is called the respiratory quotient (RQ). Depending on metabolic events, this ratio ranges from 0.7 to 1.0. The respiratory quotient thus represents the gas exchange of the lung as well as the requirements of the cells in the body. When we speak of the gas exchange ratio in the lung, in contrast to the quotient in the body cells, we usually refer to it as R (standing for respiratory exchange ratio) instead of RQ. In the lung, oxygen and carbon dioxide exchange is determined by the flows of air and blood to the alveolar capillary exchange point. The volume of flow times the amount of gas gained or lost by the air stream (or blood stream) is equal to the amount of gas exchanged. Thus, the amount of carbon dioxide given up to the atmosphere is equal to the volume-flow of air through the lungs times the difference between the expired and inspired concentrations of carbon dioxide as shown in equation 1, and the amount of oxygen carried to the tissues is equal to the volume of blood flow times the difference between arterial and venous oxygen concentrations as shown in equation 2 (see glossary of symbols in appendix):

$$1. \quad \dot{V}_{E_{CO_2}} = \dot{V}_A \times (F_{E_{CO_2}} - F_{I_{CO_2}})$$

$$2. \quad \dot{V}_{O_2} = \dot{Q} \times (C_{a_{O_2}} - C_{\bar{v}_{O_2}})$$

We can rearrange equations 1 and 2 to give us the value for flow of gas and blood according to the Fick principle:

$$3. \quad \dot{V}_A = \frac{\dot{V}_{E_{CO_2}}}{F_{E_{CO_2}} - F_{I_{CO_2}}}$$

$$4. \quad \dot{Q} = \frac{\dot{V}_{O_2}}{C_{a_{O_2}} - C_{\bar{v}_{O_2}}}$$

If we set up a ratio of ventilation to perfusion using equations 3 and 4, we arrive at equation 5, but since the respiratory quotient at the cellular level and the R at the lung level are equal to the amount of carbon dioxide produced divided by

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From the Section of Chest Diseases, Department of Internal Medicine, Yale-New Haven Medical Center.

DR. FRANK D. GRAY, JR., Associate Professor of Medicine and Director, Section of Chest Diseases.

the amount of oxygen consumed, we can substitute R for that fraction in equation 5 and develop equation 6:

$$5.\ \frac{\dot{V}_A}{\dot{Q}} = \frac{\dfrac{\dot{V}_{E_{CO_2}}}{F_{E_{CO_2}} - F_{I_{CO_2}}}}{\dfrac{\dot{V}_{O_2}}{C_{a_{O_2}} - C_{\bar{v}_{O_2}}}} = \frac{\dot{V}_{E_{CO_2}}}{\dot{V}_{O_2}} \times \frac{C_{a_{O_2}} - C_{\bar{v}_{O_2}}}{F_{E_{CO_2}} - F_{I_{CO_2}}}$$

$$6.\ \frac{\dot{V}_A}{\dot{Q}} = R \times \frac{C_{a_{O_2}} - C_{\bar{v}_{O_2}}}{F_{E_{CO_2}} - F_{I_{CO_2}}}$$

It so happens that in the normal resting subject the right hand fraction in equation 6 approximates 1, therefore the ventilation-perfusion ratio for the lung as a whole also approximates the respiratory quotient (RQ) or the lung R. However, in any given part of the lung the R may be different from the over-all RQ so long as the Rs in other parts of the lung vary in directions which allow the mean R to be equal to the RQ. Furthermore, the over-all ventilation-perfusion ratio is not tied directly to the RQ because the fractions of oxygen and carbon dioxide in the right hand expression of equation 6 can vary with changes in $\dot{V}/\dot{Q}$ while the RQ remains constant. Each gas-exchanging unit of the lung has its own R and $\dot{V}/\dot{Q}$ ratio.

The relationship can be identified more clearly by having recourse to the oxygen-carbon dioxide diagram to which we have already alluded. In order to use this diagram one must bear in mind that the total pressure of a gas mixture (usually atmospheric pressure) is distributed in accordance with the fraction that each gas constitutes of the total mixture. Thus, each gas has a partial pressure directly proportional to its fraction of the total mixture. One must also remember that as soon as air is inspired and reaches body temperature, it becomes saturated with water vapor having a partial pressure of 47 mm.Hg. Therefore the remaining mixture is atmospheric pressure minus 47 mm.Hg of water vapor pressure. Finally, oxygen and carbon dioxide do not dissociate in a linear way in blood as they do in a gas mixture, but have specific identifiable dissociation curves.

To develop the concept of the oxygen-carbon dioxide diagram it is convenient to consider first what happens when pure oxygen is breathed. After a period of time nearly all nitrogen is washed out of the body. Then, as oxygen enters the lungs, some is removed by the blood and replaced by carbon dioxide. Consequently, the farther one goes from the outside atmosphere toward the alveoli, the lower the concentration of oxygen and the higher the concentration of carbon dioxide become. The total pressure of the two gases always equals atmospheric pressure minus 47 mm.Hg of water vapor pressure. A diagram can now be constructed (Figure 1) consisting of a 45 degree right angle triangle, the vertical leg representing carbon dioxide pressure, the horizontal leg representing oxygen pressure, while the 45 degree diagonal represents any combination of oxygen and carbon dioxide which must always add up to 100 per cent of atmospheric less water vapor pressure. Since there is no other gas involved, and since we are dealing with an open system, the oxygen and carbon dioxide molecules will maintain a one-to-one ratio as they exchange. During inspiration the oxygen tension at the mouth will equal atmospheric less water vapor pressure, and there will be no carbon dioxide partial pressure. With the addition from capillary blood of each mm.Hg of carbon dioxide partial pressure, there will be one mm.Hg less of oxygen partial pressure, since they must add up to 100 per cent of atmospheric less water vapor pressure. At a point a short distance up the diagonal side of the triangle we reach the mixture of oxygen and carbon dioxide existing in the alveoli (P_A), about 40 mm.Hg carbon dioxide and 673 mm.Hg of oxygen (40 mm.Hg + 673 mm.Hg + 47 mm.Hg water vapor = 760 mm.Hg). A short distance farther up the diagonal line one sees the point representing the relative concentration of these gases in the mixed venous blood ($P_{\bar{V}}$), as it reaches the alveoli from the tissues, about 50 mm.Hg carbon dioxide and 663 mm.Hg oxygen partial pressures.

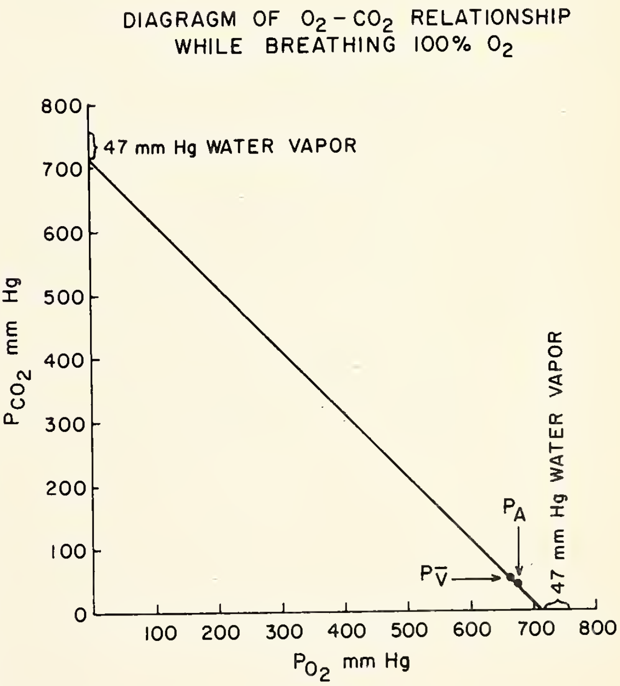

Figure I

Diagram of O_2-CO_2 relationship while breathing 100% O_2. (See glossary.)

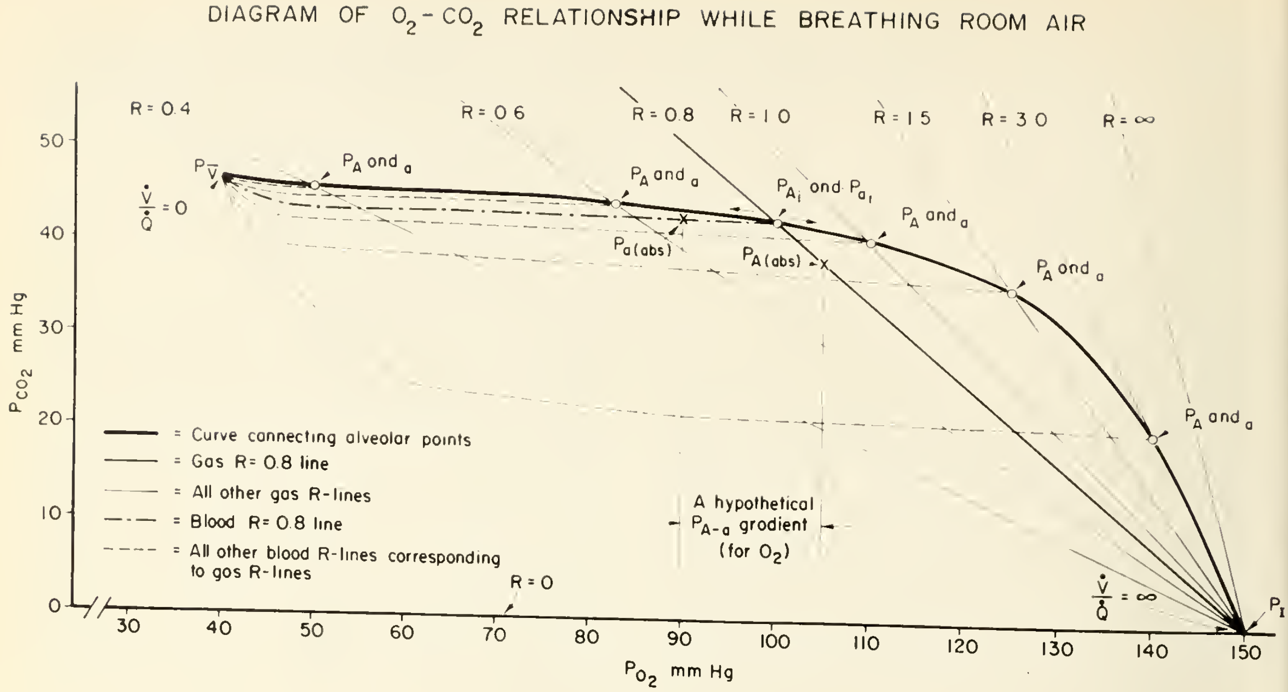

FIGURE II

Diagram of O_2-CO_2 relationships while breathing room air. (See glossary. Diagram based on Fenn et al., 1946.[1])

Now using the concept of the diagram in Figure I, we can proceed to the situation of breathing room air. Here about 79 per cent of the inspired air is nitrogen, and 21 per cent is oxygen, so we have to change the diagram as shown in Figure II. The inspired point for oxygen is now approximately 150 instead of 713 mm.Hg. As this inspired gas mixes with dead space and alveolar gas, the carbon dioxide partial pressure will rise because it is continually being supplied by the capillary blood perfusing the alveoli, and the oxygen pressure will fall owing to its diffusion into the capillary blood. If the exchange of carbon dioxide and oxygen were on a one molecule to one molecule basis, and the R were equal to 1.0, the diagonal line would again form a 45° angle as shown by the R = 1.0 line. Now, let us suppose that carbon dioxide were being produced but no oxygen removed whatever (although of course it is impossible). Then R would be equal to infinity, and the only apparent loss in oxygen tension would be due to the fact that as carbon dioxide was added, the partial pressure of both oxygen and nitrogen would have to fall to accommodate the partial pressure of the carbon dioxide. This R-equals-infinity line is shown on the right side of the diagram. The other extreme (also impossible), would be a situation in which oxygen was consumed but no carbon dioxide produced. R would now equal zero and the line would be coincident with the base line of the diagram. All actual R lines must fall between these two impossible extremes. The over-all RQ for the body in a basal state falls between the lines R = 0.7, and R = 1.0. The average RQ for the body as a whole is shown in Figure II as the line labeled R = 0.8. This means that there is not quite as much carbon dioxide produced, to be removed by ventilation through the lungs, as there is oxygen consumed, because only with the metabolism of pure carbohydrate is the ratio of carbon dioxide produced and oxygen consumed equal to 1.0.

In any particular area of the lung the R could have any value between infinity and zero, depending upon the $\dot{V}/\dot{Q}$ ratio for that local region of the lung. Accordingly, we can draw R-lines for the gas phase originating at the inspired point (P_I) for a variety of R values.

Similarly, when blood leaves systemic tissue capillaries and arrives at the beginning of the alveolar capillary, the carbon dioxide and oxygen pressures determine an R for it. As the mixed venous blood ($P_{\bar{v}}$) courses through the capillaries, the rate at which carbon dioxide is released and oxygen acquired will determine that individual alveolar-capillary R. Owing to the non-linear nature of gas dissociation in blood in contrast to the linear relationship of the partial pressures of gases in a gas mixture, the R-line is not a straight line but curved as shown by the curve $P_{\bar{v}} - P_A$. The blood and corresponding gas R-lines intersect at the alveolar points. These points represent the pressure of carbon dioxide and oxygen in end-capillary blood and alveolar air in the absence of a diffusion block. The point for the R-lines representing the respiratory quotient of the body as a whole (usually about 0.8), can be identified as the "ideal" alveolar air point P_{A_i}) of Riley and Cournand.[2]

We pointed out that the over-all $\dot{V}/\dot{Q}$ was a function of the metabolic respiratory quotient and the ratio of gas tension differences (Equation 6), but that for any local part of the lung the R was independent of the metabolic RQ. Thus, there can be both blood and gas R-lines ranging from zero to infinity. A few of these blood R-lines are plotted in Figure II. Each intersection of corresponding blood and gas R-lines produces an alveolar gas point (P_A). A curved line connecting all these points will go through every possible combination of carbon dioxide and oxygen partial pressures, from the point of inspiration (P_I) to the mixed venous blood ($P_{\bar{v}}$) as the latter arrives at the alveolar capillary.

Since the increasing ventilation expedites the removal of carbon dioxide, a high $\dot{V}/\dot{Q}$ ratio tends to promote a respiratory exchange ratio, R, approaching infinity, whereas a low $\dot{V}/\dot{Q}$ ratio leads to an R approaching zero. Therefore, as $\dot{V}/\dot{Q}$ decreases, the alveolar point moves on the heavy line toward the left or mixed venous point ($P_{\bar{v}}$) as shown by the arrow in Figure II. This represents wasted perfusion according to the terminology suggested by West,[4] and is in the direction of a venous admixture because if there were no ventilation (and $\dot{V}/\dot{Q} = O$), the alveolar air would have only the oxygen derived from mixed venous blood entering the capillary, and there would be no way of removing carbon dioxide; both gases would have the same partial pressures in the alveoli as in the mixed venous blood. On the other hand, if $\dot{V}/\dot{Q}$ rises toward infinity, the alveolar point moves to the right of the "ideal" point on the heavy curved line as shown by the right-hand arrow in figure 2 because, in the absence of perfusion, the alveolar gas cannot lose oxygen or gain carbon dioxide, and would have the same partial pressure as the inspired gas. This is equivalent to dead space ventilation or, according to West's terminology, wasted ventilation.

The lung as a whole must follow the R-line established by the metabolic RQ, but the alveolar point will be displaced as a resultant of all of the individual R-line intersection points to the right or left. *The mean alveolar and mixed venous blood*

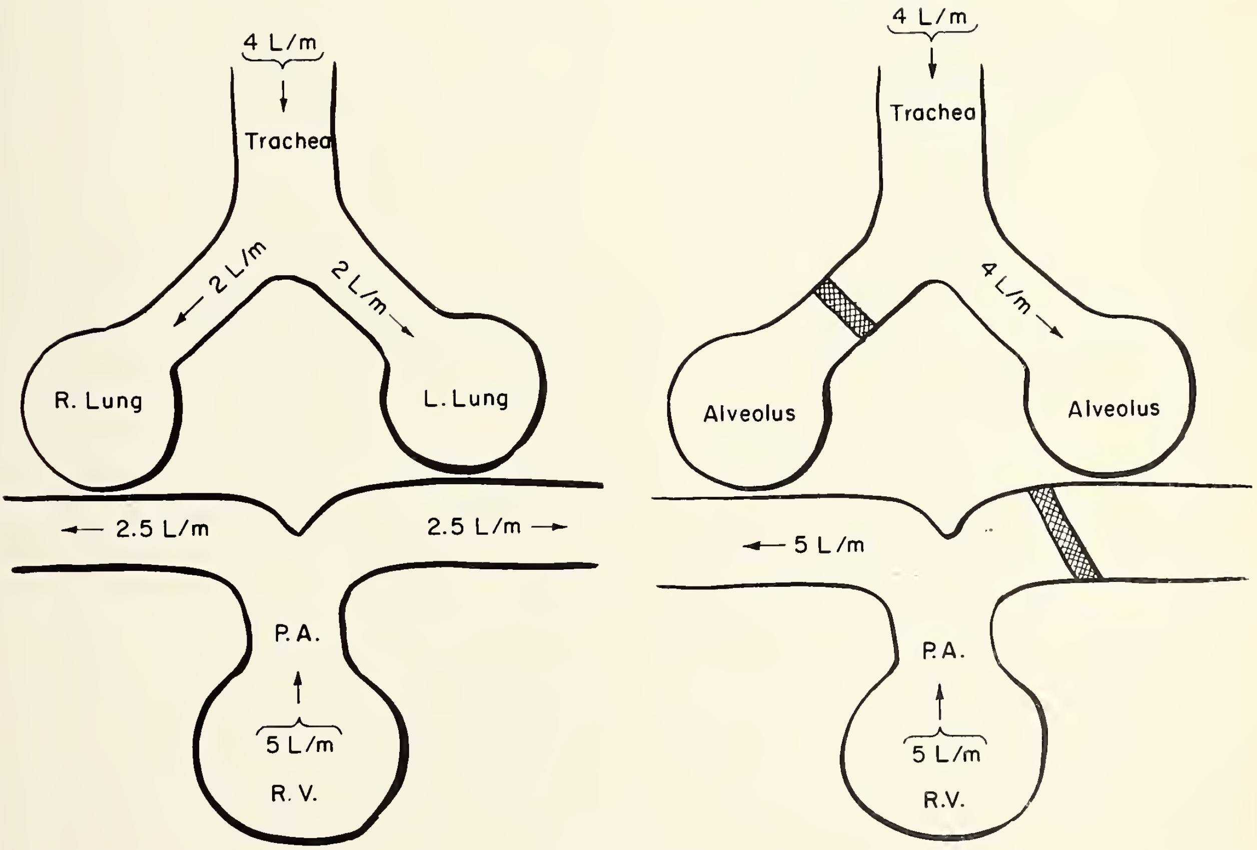

FIGURE III

A. Schematic representation of normal $\dot{V}/\dot{Q}$ ratio. (R.V. = right ventricle.) B Schematic representation of an apparently normal over-all $\dot{V}/\dot{Q}$ ratio in which actual gas exchange is nil.

gas pressures, however, will have to be plotted along the blood and gas R-lines for the body RQ (usually 0.8).

Now, with regional increase in $\dot{V}/\dot{Q}$ or wasted ventilation, the alveolar point for that region moves to the right and tends to act as a vector force pulling the mean alveolar point down along the $R = 0.8$ line for the lung as a whole, and with areas of low $\dot{V}/\dot{Q}$ or wasted perfusion (venous admixture) the end-capillary or arterial blood point moves to the left, and draws the mean arterial oxygen tension to the left along the blood R-line for the body as a whole (0.8). The horizontal difference between parallel vertical lines through the resulting alveolar (P_A) and arterial (P_a) points constitutes an alveolar-arterial blood oxygen pressure gradient. Using data for carbon dioxide, the vertical difference between parallel horizontal lines through the arterial (P_a) and alveolar (P_A) points is an alveolar-arterial carbon dioxide pressure gradient. It is evident, owing to the flat curve of the blood R-line, that carbon dioxide gradients are negligible with wasted perfusion (venous admixture), but may become significant with wasted ventilation (alveolar dead space ventilation).

When we speak of ventilation-perfusion ratios clinically, we do not refer to the overall ventilation-perfusion ratio of the entire lung because this is meaningless. Figure IIIA represents a lung in which the $\dot{Q}/\dot{V}$ ratio is 4 liters/minute divided by 5 liters/minute or 0.8, equal to the RQ of the body as a whole. Figure IIIB represents a situation in which an obstruction in the pulmonary artery diverts all five liters/minute of blood perfusion to one lung whereas a block of the contralateral bronchial airway diverts all four liters/minute of ventilation to the nonperfused lung. Here the $\dot{V}/\dot{Q}$ ratio for one lung is zero, for the other infinity, and the over-all ratio is an average of zero plus infinity, a meaningless figure. Consequently from a practical clinical standpoint we speak of the regional distribution of $\dot{V}/\dot{Q}$ ratios rather than the over-all ratio.

The actual measurement of these ratios is difficult. One method, described by West,[4] utilizes radioactive carbon dioxide. As a subject breathes this gas it is first distributed to all ventilated parts of the lung, and then is cleared by the capillary blood which carries it away from the lung. If the subject takes a single breath of the gas, and holds it for 15 seconds, scintillation counters placed in the front and back of his chest, right and left, upper and lower quadrants, will show a rise in activity as the gas reaches the alveoli, proportional to the volume of ventilation and volume of the lung in the counting field, and as the gas diffuses into the blood to be removed, the down-slope of the tracing will be proportional to the regional blood flow. Other radio-active gases have been used in this way, and by placing four or more counters in the front and back of the chest, an estimate can be made of these regional $\dot{V}/\dot{Q}$ ratios. West[4] has shown by this method that the perfusion of the normal human lung in the upright position decreases steadily from the base to the apex, as does the ventilation but the latter decreases less rapidly; therefore the $\dot{V}/\dot{Q}$ ratio is normally very high (about 3.3) at the apex, and very low (about 0.63) at the base with intermediate values in between. The equipment needed for regional studies is not generally available so, from a practical standpoint, we usually depend upon the alveolar-arterial oxygen and carbon dioxide pressure gradients ($P_{A}\text{-}a_{O_2}$ and $P_{A}\text{-}a_{CO_2}$), and dead space estimations. As indicated above, the gradients can be considered as vector results of opposing forces from high and low $\dot{V}/\dot{Q}$ ratios (Figure II). If the dominant alteration is a high $\dot{V}/\dot{Q}$ ratio, the alveolar point tends to be displaced to the right along the average gas R-line, and consequently the $P_{A}\text{-}a_{O_2}$ gradient will be wide because the alveolar oxygen pressure ($P_{A_{O_2}}$) rises while the arterial oxygen pressure ($P_{a_{O_2}}$) remains approximately normal. If the predominant $\dot{V}/\dot{Q}$ abnormality is low, it will tend to displace the arterial oxygen point to the left along the average blood R-line producing a wide $P_{A}\text{-}a_{O_2}$ gradient, the arterial oxygen pressure ($P_{a_{O_2}}$) tending to be low while the alveolar oxygen pressure ($P_{A_{O_2}}$) remains normal. More often there will be a combination of high and low ratios so that the alveolar point is shifted to the right and the arterial point to the left leading to a very wide $P_{A}\text{-}a_{O_2}$ gradient. On the other hand, in the presence of severe impairment of perfusion, with the resulting displacement of the alveolar point to the right and down along the gas R-line, there will also be a widening of the $P_{A}\text{-}a_{CO_2}$ pressure gradient. This occurs in pulmonary embolism. The influence of $\dot{V}/\dot{Q}$ on gradients can be summarized by saying that the $\dot{V}/\dot{Q}$ abnormality leading to increase in alveolar dead space (such as in pulmonary embolism) displaces the alveolar point in such a way that both oxygen and carbon dioxide alveolar-arterial pressure gradients are widened, whereas when the $\dot{V}/\dot{Q}$ inequality is of such a nature as to increase the venous admixture, the oxygen alveolar-arterial pressure gradient is widened but the carbon dioxide gradient is only negligibly affected.

The overall effects of $\dot{V}/\dot{Q}$ inequalities in various clinical syndromes are shown in Fig. IV. However, this figure is only a general guide and any combination may occur in any disease. It must be emphasized that the $\dot{V}/\dot{Q}$ concept should be used only to describe regional phenomena which influence

CLINICAL SYNDROME	$P_{A_{O_2}}$	$P_{A_{CO_2}}$	$P_{a_{O_2}}$	$P_{a_{CO_2}}$	$P_{A-a_{O_2}}$	$P_{A-a_{CO_2}}$
I. PREDOMINANTLY LOW $\dot{V}/\dot{Q}$	→ or ↓	↑	↓	↑	↑	→
EMPHYSEMA						
BRONCHITIS						
NEUROMUSCULAR DISEASE	*					
II. PREDOMINANTLY HIGH $\dot{V}/\dot{Q}$	↑	↓	→	↓	↑	↑
PRIMARY PULMONARY HYPERTENSION						
"BLOOD LOSS" SHOCK						
PULMONARY EMBOLISM						
III. COMBINATIONS OF I AND II	↑ or ↓	↑ or ↓	↓	→ or ↓	↑	→
INTERSTITIAL PNEUMONIA						
(ALVEOLAR-CAPILLARY BLOCK) **						

FIGURE IV

Table of clinical counterparts of $\dot{V}/\dot{Q}$ ratios with associated blood gas changes.

* = In severe neuromuscular disability $\dot{V}$ falls and $\dot{Q}$ may rise leading to a $\dot{V}/\dot{Q}$ approaching zero or almost pure venous admixture in which, transiently, O_2 may be lost from capillary blood to non-ventilating alveoli.

** = Most of the gas exchange abnormality in alveolar-capillary block can be explained by $\dot{V}/\dot{Q}$ inequality; a block to gas diffusion is a theoretical but very small component.

These concepts apply to sea level breathing. For analysis of the problems at high altitude, see Rahn and Fenn.[5] When lung structure is normal and hypoventilation diffuse, P_A and P_a for both O_2 and CO_2 change concomitantly and the gradients remain nearly normal. This is not shown on the above chart.

total lung function; it is not a measure of total lung function.

Impairment of diffusion between alveolar space and capillary space is rarely a significant factor, but it can be accounted for in this scheme as a decrease in the $\dot{V}/\dot{Q}$ ratio since with normal ventilation, there is no block.

The ventilation-perfusion ratio concept is a useful way of thinking about pulmonary impairment. At the present time available methods of estimating the ratio are either very complicated, or indirect. The concept is useful, nonetheless, because it helps us focus our thinking on the established principles underlying the movement of oxygen and carbon dioxide between the atmosphere and the tissues. It gives especial importance to the absolute necessity for the inhaled gas molecules and the blood perfusing the pulmonary airways to meet with optimal rates and concentrations. It also helps us account for both normal and pathological variations in blood gas concentrations that may, at first glance, seem discordant with our idealized concept of the structural characteristics of the lung.

APPENDIX

Glossary

$\dot{V}_{E_{CO_2}}$ = Minute volume of expired carbon dioxide.

$\dot{V}_A$ = Minute volume of alveolar ventilation.

$F_{E_{CO_2}}$ and $F_{I_{CO_2}}$ = Fractions of expired and inspired carbon dioxide in air respectively.

$\dot{V}_{O_2}$ = Minute volume of oxygen utilized.

$\dot{Q}$ = Minute volume of blood flow.

$C_{a_{O_2}}$ and $C_{\bar{v}_{O_2}}$ = Concentrations of arterial and mixed venous blood oxygen respectively.

P_A = Alveolar partial pressure of a gas.

P_a = Arterial blood partial pressure of a gas.

P_{A_i} and P_{a_i} = Ideal alveolar and arterial partial pressures of a gas.

P_I = Partial pressure of a gas on inspiration.

$P_{\bar{v}}$ = Partial pressure of mixed-venous blood gas.

$P_{A(OBS)}$ or $P_{a(OBS)}$ = Partial pressures of gases actually observed.

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(The first three references are of historical interest and present admirable examples of applying theoretical concepts to practical problems, while the fourth reference is recommended as an excellent source for the reader who wishes further information on this subject.)

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Pulmonary Function In Surgical Patients

George J. Horner, M.B., B.S.

■ An ever increasing progress in surgical techniques and patient care enables a great number of major surgical procedures to be undertaken on patients who, not so long ago, would have been considered a grave risk. The increasing number of operations in the aged and the trend toward more extensive surgical procedures places an even greater responsibility upon the physician to be aware of changes which often may pass unrecognized in both pre- and post-operative periods. Many studies have been undertaken and still are being conducted to determine and clarify some of the mechanisms leading to impaired respiratory function in relation to surgery.

Some disturbance of respiratory function will be found in every patient during and after surgery. There are, however, a few groups of patients where such a deficit will be of much greater significance.

Patients with a pre-existing cardiopulmonary disease may have a lower than normal arterial oxygen tension; an excessive production of secretions; retention of carbon dioxide; high work of breathing; and, reduced potential ventilatory compensation.

Obese patients have a higher than normal respiratory exchange (increased oxygen consumption and carbon dioxide production), therefore their effective ventilation has to be higher to maintain a normal arterial blood gas tension. In these patients a more positive abdominal pressure and a more elevated diaphragm in recumbancy leads to a considerably diminished expiratory reserve volume, and moving the chest wall with relatively inefficient respiratory muscles requires a considerable increase in the work of breathing, especially in the horizontal position.

Many aging patients have been described as having some reduction in arterial oxygen tension, a diminished diffusing capacity, an unusually uneven ventilation-perfusion ratio, and changes in lung volumes and capacities (reduction in vital capacity and expiratory reserve volume, increase in residual volume, and increase in dead space). Both circula-

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tory and ventilatory compensatory responses to hypoxia may be diminished in old people, and hypoxemia leads more quickly to tissue hypoxia because of insufficient compensation by the heart.

In addition to the above mentioned groups of patients the following factors contribute to the potential risks of surgery.

Drugs

Barbiturates, morphine, and meperidine, examples of drugs commonly used both in pre-operative medication and in the post-operative period to relieve pain, are respiratory depressants.

Atropine and scopolamine decrease secretions in the respiratory tract but with their use the mucus thickens and may be difficult to cough up.

General anesthetic agents depress the response of the respiratory center to carbon dioxide and hydrogen-ion. In addition, cyclopropane may cause bronchoconstriction, and ether excessive respiratory tract secretions.

Spinal anesthetic agents can cause hypoventilation by blocking or depressing nerve conduction to abdominal and intercostal muscles.

Neuromuscular blocking agents (tubocurarine, succinyl choline, decamethonium, etc.), usually depress the neuromuscular junction of respiratory muscles while producing relaxation of abdominal or skeletal muscles. In addition, tubocurarine may produce bronchoconstriction by liberating histamine.

Rauwolfia alkaloids, used in some patients to control hypertension, act by partly depleting the catecholamine stores in the body. In this fashion the circulatory compensatory response to hypoxia is reduced and there is an increased danger of myocardial depression and hypotension when anesthesia is administered in such patients.

Phenothiazines (e.g. Chlorpromazine) posses antiadrenergic effects, and patients having received this drug will frequently develop hypotension during anesthesia, have a decreased sympathetic compensatory response in hypoxia and decreased response to exogenous catecholamines.

Prolonged *corticosteroid therapy* tends to suppress endogenous secretion of corticosteroids; this will result in a decreased response to catecholamines and a diminished circulatory compensation to hypoxia during operation and in the postoperative period. The potential danger of circulatory collapse in such patients should be anticipated and an increased corticosteroid dosage provided to cover the critical period.

Pain

Pain from the operative site in the abdomen or chest interferes with the free movement of the chest and the use of the abdominal muscles for coughing. The restrictive influence on ventilation so imposed may lead to shallow breathing and a consequent atelectasis; ineffective cough and retained secretions will lead to pulmonary infection. The degree of impaired ventilatory function will be determined by the site of the incision. Thus surgical procedures outside the chest and abdomen do not interfere with respiratory function but vital capacity is reduced considerably following surgery of the lower abdomen and more so in surgery of the upper abdomen. Other effects of abdominal surgery on respiratory function include an increase in respiratory rate, decreased tidal volume, and a reduction in inspiratory capacity and reserve volume.

Abdominal Distention

Abdominal distention with the consequent increase in intra-abdominal pressure causes reduction in lung volumes and capacities. It is a frequent cause of respiratory complications post-operatively.

Restrictive Dressing

This acts in a way similar to abdominal distention in interfering with respiratory motion and decreasing available ventilatory compensation.

Smoking

In heavy smokers (more than one package of cigarettes per day), even without an established diagnosis of a chronic obstructive lung disease, the incidence of post-operative respiratory complications is significantly higher than among nonsmokers.

Position

Even in healthy subjects the arterial oxygen tension is slightly lower in the supine than in the erect position, and lung volumes and capacities are reduced in the supine position. The horizontal position also leads to changes in distribution of ventilation as well as perfusion, resulting apparently in a less favorable ventilation-perfusion ratio, which may explain the slightly lower arterial oxygen tension.

Anemia

It is not uncommon for a hospitalized patient to have a low hemoglobin content which may remain uncorrected. This reduced oxygen carrying capacity of the blood has to be compensated by increase in oxygen transport per minute, i.e. an increase in cardiac output. The higher inspired oxygen concentration may not be an adequate substitute for reduced hemoglobin content; in fact, one unit of packed cells will accomplish more than the use of 100 per cent oxygen in an anemic but otherwise normal individual.

The factors listed above may produce hypoxemia in several ways:

Hypoventilation which will lead to both low arterial oxygen tension and a high carbon dioxide tension with respiratory acidosis.

Increased venous admixture (or shunt) which is defined as that part of the cardiac output which is returned to the left heart unoxygenated:

(1). Uneven distribution of ventilation in relation to perfusion is a cause of shunting whenever some alveoli are hypoventilated relative to their perfusion.

(2). Atelectasis is a non-ventilating air space presumably in a state of collapse. If such a non-ventilated air space remains perfused a venous admixture or shunt is established. This venous admixture is independent of alveolar oxygen tension and its recognition is facilitated by its persistence even when 100 per cent oxygen is breathed.

When ventilating spontaneously or artificially at constant tidal volumes diffuse atelectasis may develop with decrease in lung volume, decreased compliance, and increased venous admixture. These changes may be reversed by occasional deep breaths. A normal person sighs approximately nine times per hour. Drugs, pain, and immobility all limit the frequency and extent of such sighing. The collapse of the alveolar unit may be due to behaviour of surface forces acting at the gas-liquid interface of alveolar units. A film (surfactant) reduces surface tension when the alveolar volume is decreased and thus provides stability to the lung by allowing alveolar units to exist in an inflated state at low transpulmonary pressures and alveolar units of different sizes to exist simultaneously at the same transmural pressure. However, when not moved or stretched this surfactant exhibits "ageing", i.e. the surface tension increases when the surface film is inactive. Alveolar units with increased surface tension will decrease in size and tend to collapse. Atelectatic areas, being poorly drained, may be good areas for infection to occur. Most, if not all, post-operative pneumonias begin as atelectasis.

Because hypoxemia still appears to be a major clinical problem in patients during and after surgery, recognition of all factors which may promote hypoxia or interfere with compensatory mechanisms is mandatory. Pre-operative evaluation of pulmonary function in all patients suspected of ventilatory disturbance should be planned; in the presence of obstructive pulmonary disease a vigorous bronchial toilet including intermittent positive pressure breathing, bronchodilators, postural drainage and breathing exercises should be undertaken for several days before surgery. During and after operation a free use of blood gas analysis and pH estimation should be made for guidance through potentially stormy post-operative periods in selected cases.

Summary

The pre- and post-operative period, as well as the surgery itself, carries an increased hazard to ventilatory function in certain groups of patients. Recognition of the factors playing part in this potentially dangerous period may mean a difference between a smooth and uneventful post-operative course, and a stormy one with serious complications.

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Usefulness Of Serial Arterial Blood Gases In The Care Of Patients With Respiratory Failure

Byong Mok Kim, M.D.

■ Since the Severinghaus carbon-dioxide and Clark oxygen tension electrodes became available, the measurement of the arterial blood gases has become easier and relatively less time consuming. The measurement of arterial blood gases should include not only oxygen tension (PO_2) and carbon dioxide tension (PCO_2) but also pH determinations.

A definition of respiratory failure has been proposed by Bates and Christie[1]: " 'respiratory failure' may be said to be present when the tension of respiratory gases in the blood leaving the lungs is no longer within physiological limits." This definition is broad; the American Thoracic Society, in its statement on principles of respiratory care[2], states more specifically that, although considerable insufficiency for oxygenation and carbon dioxide removal may be tolerated, patients with oxygen tensions persistently below 55 mmHg or carbon dioxide tensions above 50 mmHg are in respiratory failure and usually require respiratory care. Thus, serial arterial blood gas determinations are an invaluable part of the critical assessment of patients with respiratory failure since these tests define the initial state of respiratory failure as well as the subsequent dynamic changes due to the therapeutic management. As is evident from the above definitions, carbon dioxide retention indicates respiratory failure primarily due to alveolar hypoventilation, and moderate to severe hypoxemia without hypercapnia may indicate a more critical respiratory failure due to the effect of venous admixture. It is further stated by Bates and Christie[3] that in their experience, there can be no substitute for the measurement of arterial gas tension in the diagnosis and management of respiratory failure. For the analysis of hypercapnia a PCO_2 of $\geqslant 45$ mmHg was chosen as a sign of alveolar hypoventilation.

Any abnormalities in pulmonary function due to various etiological factors should be reflected in arterial blood gas tensions. The lungs can be treated as the organ for removing carbon dioxide from mixed venous blood and picking up oxygen for arterial blood. Thus, the abnormalities of arterial blood gas tensions can be categorized into three general groups: I) hypercapnia with compensated or uncompensated respiratory acidosis and concomitant hypoxia; II) hypercapnia with alkalosis and concomitant hypoxia; and III) hypoxia with respiratory alkalosis or metabolic acidosis. From a clinical point of view these three groups offer certain categories of patients with respiratory failure: group I includes a majority of chronic obstructive pulmonary diseases with or without acute exacerbation; group II includes chronic obstructive pulmonary diseases with concomitant metabolic alkalosis due to hypokalemia, hypochloremia, or too rapid reduction of PCO_2 by mechanical ventilation; and, group III includes diffuse or focal restrictive pulmonary disease with a venous admixture effect due to various causes. Physiologically, groups I and II have abnormalities in alveolar hypoventilation due to impaired ventilation and uneven distribution of inspired gas. Group III, however, consists primarily of abnormalities in the diffusion of oxygen, perfusion of mixed venous blood and ventilation-perfusion inequality.

At the Yale-New Haven Hospital the number of arterial blood gas measurements on patients increased nearly ten fold from 1963 to 1966. The number of arterial bloods with a $PaCO_2$ of $\geqslant 45$ mmHg also increased from 95 in 1963 to 806 in 1966. In 1963, 168 patients had a total of 308 arterial blood gas analyses, whereas in 1966, 940 patients had a total of 3088 arterial blood gas analyses. The number of patients who had $PaCO_2$ of $\geqslant$ 45 mmHg represented 12 per cent of all patients who had arterial blood gas analyses in 1963, whereas in 1966, 20 per cent of all patients who had the arterial blood gas analyses had hypercapnia of $PaCO_2 \geqslant 45$ mmHg. It is of note that in 1963 the average patient with hypercapnia had a series of 2.5 tests, whereas in 1966 this increased to 4.3.

Figures I, II, and III represent graphical distributions of blood samples with $PaCO_2 \geqslant 45$ mmHg for the years 1963, 1964 and 1965. For 1966

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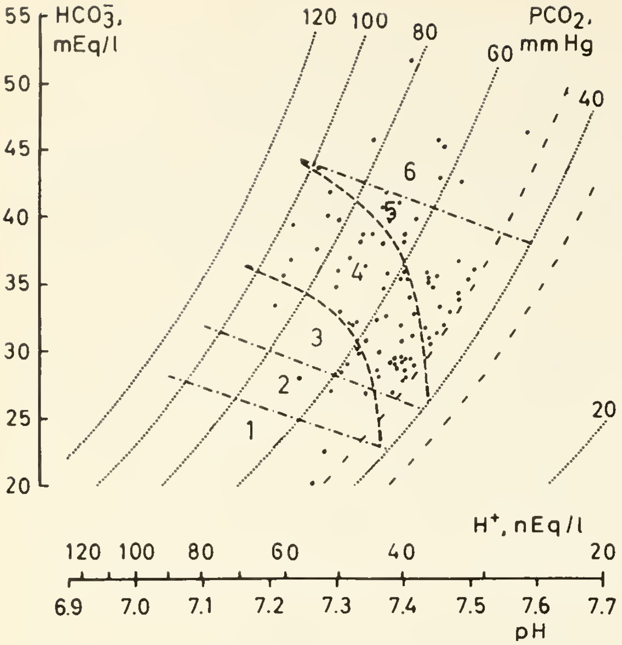

FIGURE I

Arterial blood with $PaCO_2 \geqslant 45$ mmHg for 1963 plotted in Refsum's diagram: each point plotted with arterial pH and $PaCO_2$. The numbered zones are defined in the text.

the data are too numerous for graphical representation, but they are shown on Table I.

Groups I and II represent arterial blood studies with hypercapnia of $PaCO_2$ of $\geqslant 45$ mmHg in this analysis. According to this analysis, group I includes arterial blood values which fall in Refsum's zones 1, 2, 3 and 4, and group II includes those in zones 5 and 6. The majority of group I falls in zone 4 which represents a zone of chronic compensated respiratory acidosis. In 1963, 52.7 per cent were distributed in zone 4, whereas in 1966 only 36.4 per cent fell into this category. However, there is an increasing percentage, annually, for zone 1 which represents a frank superimposed metabolic acidosis with hypercapnia. Zone 1 includes those arterial blood gas tensions in cases of severe metabolic acidosis due to cardiogenic shock and terminal hypercapnia. The increasing incidence in zone 1 represents more vigorous management of terminal cardiac patients with defibrillation and external cardiac massage. Zone 2 is defined as a zone of acute uncompensated respiratory acidosis paral-

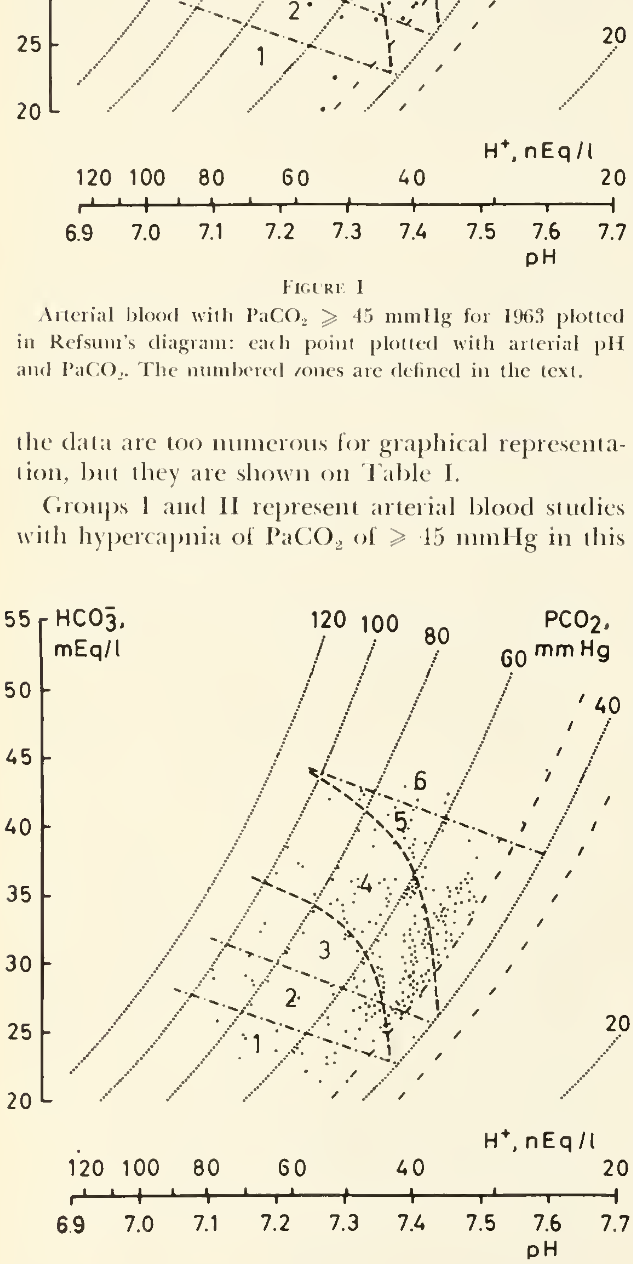

FIGURE II

Arterial blood with $PaCO_2 \geqslant 45$ mmHg for 1964 plotted in Refsum's diagram: each point plotted with arterial pH and $PaCO_2$.

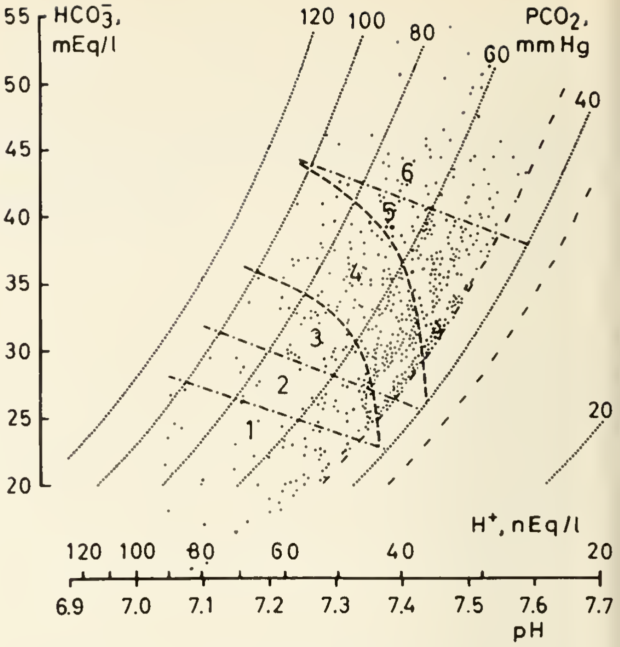

FIGURE III

Arterial blood with $PaCO_2 \geqslant 45$ mmHg for 1965 plotted in Refsum's diagram: each point plotted with arterial pH and $PaCO_2$.

TABLE I

DISTRIBUTION OF ARTERIAL BLOODS WITH PCO_2 OF $\geqslant 45$ mmHg ON REFSUM'S DIAGRAM
(For Year 1966)

Zone	*No.*	*Per Cent*
1	110	13.6%
2	111	13.6%
3	62	7.7%
4	294	36.4%
5	168	20.8%
6	61	7.9%
Total	806	100 %

leling body buffer lines, and zone 3 is an intermediary zone between zones 2 and 4 and defined as either partially compensated acute respiratory acidosis or a superimposed respiratory acidosis on chronic compensated respiratory acidosis. Zone 4 is a compensated respiratory acidosis. Group I, falling in zones 1, 2, 3, and 4 remained fairly constant at 60-70 per cent of all tests, showing $PaCO_2$ of $\geqslant 45$ mmHg throughout the four years.

Group II studies lie in zones 5 and 6, and constitute 30-40 per cent of tests showing a $PaCO_2$ of $\geqslant 45$ mmMg annually. Zone 5 is defined as a zone of acute recovery from compensated respiratory acidosis, or a metabolic alkalosis superimposed on compensated respiratory acidosis. Zone 6 is defined as a frank metabolic alkalosis superimposed on compensated respiratory acidosis. There has been an increasing incidence of tests in zone 6 in the last two years.

Case History, Group I

H.C. a 62-year-old white male was admitted on 25 September 1965 and expired on 16 October 1965. He had 30 aterial blood gas studies during his hospital course. The initial tests on 25 September 1965 revealed that pH = 7.16, $PaCO_2$ = 83 mmHg, and PaO_2 = 62 mmHg (O_2 therapy) with venous serum electrolytes of Na = 136, K = 3.9, Cl = 89 and HCO_3 = 30.5 mEq/L. These data fall in Refsum's zone 2. Subsequently the patient was tracheostomized and treated vigorously with I.P.P.B. and oxygen. The next day the arterial blood gas study revealed that pH = 7.38 and $PaCO_2$ = 59 mmHg which now fell in zone 4. This is in accordance with an initial Cl of 89 and HCO_3 of 30.5 mEq/L. suggesting chronic renal compensatory mechanisms at play, thus, as the $PaCO_2$ decreased from 83 to 59 mmHg by I.P.P.B. via tracheostomy, the initial point in zone 2, which represents an acute respiratory acidosis superimposed on chronic compensated respiratory acidosis, shifted to zone 4 which represents a chronic compensated respiratory acidosis. Five days later a repeated arterial blood gas study revealed a pH of 7.47, $PaCO_2$ of 58 mmHg and PO_2 of 35 mmHg (breathing ambient air) with venous serum electrolytes of Na = 139, K = 4.2, Cl = 85 and HCO_3 = 39.5 mEq/L. These data shift the point to zone 5 which represents acute recovery from chronic compensated respiratory acidosis and superimposed metabolic alkalosis. The latter occurred because the patient had gastric distension with bleeding treated by gastric aspiration, Amphogel, and milk. On the seventh day the pH was 7.48, and $PaCO_2$ 73 mmHg with venous serum electrolytes of Na = 140, K = 3.5, Cl = 82 and HCO_3 = 40.0 mEq/L. The acid-base point was shifted farther to zone 6 which represents superimposed metabolic alkalosis on acute and chronic respiratory acidosis. On the 21st hospital day the patient expired from massive upper gastro-intestinal bleeding despite rapid blood transfusion. This case illustrates a dynamic shift in acid-base balance in the management of acute and chronic respiratory failure with hypercapnia and the importance of superimposed metabolic acid-base changes which may influence the final outcome. The plotting of pH and $PaCO_2$ serially on Refsum's diagram was helpful not only in assessing various factors influencing the acid-base balance at each moment but also to provide a vectorial assessment of the over-all management of acid-base balance in a complicated case.

Case History, Group II

W.C., a 64-year-old white male was transferred from another hospital on August 1, 1963 with severe dyspnea. He had initial arterial blood gas studies with a pH of 7.47, $PaCO_2$ 64 and PaO_2 35 mmHg and oxygen saturation of 71 per cent. These data place the initial point in zone 6. The patient had been treated for congestive heart failure with digitalis, chlorothiazide and mercurial diuretics in the first hospital. On the day after transfer following vigorous I.P.P.B. therapy, the PCO_2 dropped to 57 mmHg but the pH became more alkalotic at 7.49. At this time venous serum electrolytes revealed that Na = 137, K = 3.5, Cl = 86 and HCO_3 = 39 mEq/L. Clearly this patient had chronic respiratory acidosis with superimposed metabolic alkalosis manifested by hypochloremia. A pH of 7.48, and PCO_2 of 51 indicated a shift in the initial point to zone 5 after nine days of vigorous I.P.P.B. therapy. In order to correct a component of metabolic alkalosis, 1,000 ml. of saline containing 40 mEq of KCl were given intravenously on the ninth day. The next day a pH of 7.43, PCO_2 of 45 mmHg and PO_2 of 68 mmHg were obtained with Na of 137, Cl of 94 and HCO_3 of 29.2 mEq/L, thus correcting the pH to the upper limit or normal. These data shift the point farther down to zone 4 which represents a chronic compensated respiratory acidosis for this patient. This case illustrates persistent alkalosis in spite of a decreasing $PaCO_2$ with vigorous I.P.P.B. therapy, until superimposed metabolic alkalosis was corrected with KCl[5].

Group III Problems

Serial determinations of PaO_2 with oxygen and mechanical ventilation provide guidelines for the successful management of patients in the Group III category. The patients with acute or chronic restrictive pulmonary disease such as sarcoidosis, diffuse interstitial pneumonia, and diffuse pulmonary fibrosis fall into this category, as well as those with acute respiratory failure following prolonged extracorporeal oxygenation or massive atelectasis as a complication of upper abdominal surgery. In order to correct severe hypoxia, initially high oxygen concentration with effective mechanical ventilation is required; however, as hypoxia improves the inspired oxygen concentration should be reduced below 40 per cent to prevent the pathological changes due to prolonged exposure to high oxygen concentration.[6] As soon as PaO_2 exceeds 150 mmHg with oxygen and mechanical ventilation, the inspired oxygen concentration is reduced to provide a PaO_2 of around 80-100 mmHg. On the other hand, we have encountered several cases of fulminating interstitial pneumonia with severe hypoxia which could not be corrected adequately with 100 per cent oxygen and mechanical ventilation, resulting in moderate to severe respiratory alkalosis. These patients may be benefitted by extracorporeal oxygenation during the initial period of severe hypoxia, which cannot be corrected with 100 per cent O_2 and currently available mechanical ventilators despite the resulting respiratory alkalosis.

Case History, Group III

G.W., was admitted with acute pancreatitis on October 10, 1966, and treated with nasogastric suction and intravenous electrolyte replacement uneventfully for 10 days when shock and cyanosis developed. Arterial blood gas studies at this time revealed a pH of 7.22, PCO_2 of 41 mmHg and PO_2 of 44 mmHg with an arterial oxygen saturation of 70 per cent. The patient was found to have a pseudocyst of the pancreas and left pleural effusion. During the next eight hours the patient was ventilated by a volume limited mechanical ventilator and 100 per cent oxygen via tracheostomy. Arterial blood gas studies revealed a pH of 7.44, PCO_2 of 41 mmHg and PO_2 of 50 mmHg with the correction of shock by vasopressor agents. After vigorous I.P.P.B. therapy and 100 per cent oxygen, arterial blood gas studies revealed a pH of 7.50 and PCO_2 of 31 mmHg, but the PO_2 was still 44 mmHg despite a moderate respiratory alkalosis. This case exemplifies the difficulty of correcting severe hypoxia due to venous admixture or the shunting effect of mechanical ventilation.

Acknowledgement

I would like to acknowledge my appreciation to Mr. Ernest Festa who did most of the arterial blood gas and pH determinations.

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Clinical Physiology Of Respiratory Failure

George J. Horner, M.B., B.S.

■ The major function of the cardio-respiratory system is to provide an adequate amount of oxygenated blood at each moment to all tissues of the body. The primary function of the lung is to provide oxygen for venous blood and to remove the waste product, carbon dioxide. The efficacy of this system is reflected in the tension of respiratory gases leaving the lung.

An interference with the gas exchange at any level severe enough to cause hypoxia and/or hypercapnia will lead to respiratory failure. This can occur in normal lungs as well as in association with lung disease, and the factors most commonly involved are hypoventilation, inequality of the distribution of ventilation and perfusion ratios, and poor diffusion.

Hypoventilation

Inadequate ventilation of alveoli is one of the most frequent causes of a deficient gas exchange resulting in hypoxemia, carbon dioxide retention, and respiratory acidosis. (Alveolar ventilation is that part of total ventilation which participates in gas exchange; the remaining volume of air fills the conducting airways and nonperfused alveoli-physiological dead space. A pathological and uncompensated increase in dead space or reduction in tidal volume will result in hypoventilation).

The oxygen requirement at rest is approximately 250 ml. per minute. In hypoventilation the oxygen supplied is inadequate to maintain normal alveolar levels of the gas, thus the oxygen tension in the pulmonary capillary blood perfusing the hypoventilated alveoli will fall, with a consequent decrease in arterial oxygen tension and saturation. At the same time there will be a rise in alveolar and arterial carbon dioxide tensions because the decreased volume of air ventilating the alveoli will be insufficient to remove all the carbon dioxide produced and brought to the alveoli by the venous blood. Such an elevation in carbon dioxide tension will cause a fall in pH with respiratory acidosis as a result.

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TABLE I
CAUSES OF HYPOVENTILATION

I. THORACIC
  A. Extrapulmonary
    1. Bony Cage
      (a) Arthritis.
      (b) Deformities.
      (c) Scleroderma.
    2. Respiratory muscles
      (a) Elevation of diaphragm.
      (b) Muscle dystrophies.
      (c) Neuromuscular block
        (1) curare, succinylcholine, decamethonium.
        (2) nerve gases.
        (3) botulinus, and nicotine poisoning.
        (4) myasthenia gravis.
      (d) Infections
        (1) poliomyelitis.
        (2) peripheral neuritis.
      (e) Spinal cord trauma.
    3. Pleural Space
      (a) Pleural effusion.
      (b) Pneumothorax; hemothorax.
  B. Pulmonary
    1. Decrease in Functioning Lung Tissue
      (a) Atelectasis.
      (b) Tumor.
      (c) Pneumonia.
    2. Decreased Distensibility of Lung Tissue
      (a) Restrictive disease.
      (b) Congestion.
    3. Obstruction
      (a) Smothering (externally applied occlusion.)
      (b) Malposition of tongue during unconsciousness.
      (c) Foreign body.
      (d) Excessive secretions.
      (e) Laryngeal spasm and paralysis (e.g. bulbar poliomyelitis).
      (f) Edema and swelling due to inflammation of tracheobronchial tree.
      (g) Mucous plug.
      (h) Space occupying lesions involving tracheobronchial tree.
II. CENTRAL NERVOUS SYSTEM
    1. Intracranial Space-occupying Lesions
      (a) Expanding tumor.
      (b) Trauma with hemorrhage.
      (c) Inflammatory swelling.
      (d) Defective cerebrospinal fluid absorbtion.
    2. Direct Trauma to Medulla.
    3. Virus Infections (e.g. Bulbar Poliomyelitis.)
    4. Drugs
      Decrease sensitivity of respiratory center to CO_2 and depress intrinsic CNS mechanism of respiration.
      (a) General anesthesia.
      (b) Barbiturates.
      (c) Morphine.
      (d) CO_2 Narcosis.
    5. Hypoxia or Cerebral Ischemia.
    6. Metabolic Alkalosis.
    7. Electrocution.

There is a wide variety of factors contributing to or causing hypoventilation (Table I), however they all converge upon a final common pathway towards hypoxemia, hypercapnia, and acidosis.

Uneven Distribution Of Ventilation And Blood Flow

An ideally functioning lung would be one where the inspired air is uniformly distributed to each of the alveoli with all the alveolar units evenly perfused by blood. In such a case the ventilation/perfusion ratio would be equal in every part of the lung. In reality there is a regional unevenness of ventilation/perfusion ratios even in a normal lung ranging from the under-perfused (and relatively over-ventilated) apex to the over-perfused (and relatively under-ventilated) base. In spite of these regional differences, the net effect of this ventilation/perfusion ratio inequality on over-all gas exchange is minimal, resulting in a reduction of arterial oxygen tension by only approximately 3 mm.Hg below that which would be present in an ideally functioning lung.[1]

In an abnormal lung, however, the inequality of ventilation in relation to perfusion may be such as to cause a significant impairment of gas exchange. Two extreme examples of such inequality are:

1. *Venous admixture* (shunt) which is that part of the blood which perfuses non-ventilating alveoli (e.g. in atelectasis, consolidation, terminal airway closure), and consequently does not take part in gas exchange. It joins the arterialized blood and lowers the mean arterial oxygen tension.

2. *Alveolar Dead Space* signifies that volume of air which ventilates non-perfused alveoli (e.g. in pulmonary embolism, emphysema, destruction of part of the pulmonary vascular bed).

Diffusion

Oxygen diffusion from alveoli to pulmonary capillary blood may be reduced in conditions such as sarcoidosis, berylliosis, asbestosis, pulmonary edema, interstitial or alveolar pulmonary fibrosis and emphysema where there is destruction of alveoli and capillaries. The resulting impairment in gas exchange will lead to hypoxemia without hypercapnia.

Effects Of Hypoxemia

The fall in arterial oxygen tension stimulates carotid and aortic body chemoreceptors to a reflex increase in tidal volume and respiratory rate. The significant response occurs at an arterial oxygen tension of less than 60 mm.Hg. This reflex works even in unconsciousness responding only to a fall in arterial oxygen tension and not to content (i.e. does not work in anemia, methemoglobinemia, or carbon monoxide poisoning.[2]

The brain is very sensitive to oxygen deprivation. Increased permeability to passage of water occurs in brain capillaries even in hypoxia of brief duration and cerebral edema develops. Irreversible parenchymal damage can occur rapidly. Chronic hypoxia of moderate degree may produce impairment of judgment, psychologic abnormalities and increased neuromuscular irritability.[3]

The pulmonary arterial bed reacts to hypoxia by vasoconstriction, increased resistance to blood flow with a consequent pulmonary hypertension and ultimately right ventricular failure.

Centrilobular liver cells may undergo fibrosis in moderate, prolonged hypoxia. In profound hypoxia portal hypertension and frank hepatic necrosis may occur.

Effects Of Hypercapnia

The elevation of arterial carbon dioxide tension stimulates the respiratory center to a rise in tidal volume and respiratory rate. However, drugs (barbiturates, morphine, anesthetic agents), severe hypoxia and hypercapnia, will depress the respiratory center and no response will occur. The manifestations due to the effect of increased carbon dioxide tension on the central nervous system resemble those of organic brain disease or tumor including papilledema, headache and somnolence.

Acidosis

A fall in pH may cause an increase in tidal volume and respiratory rate. Renal excretion of hydrogen ion is stepped-up and bicarbonate is conserved to compensate for the rise in the hydrogen ion concentration of respiratory acidosis.

In severe hypoxia an accumulation of lactic acid causes a metabolic acidosis. This is due to increased anaerobic over aerobic metabolism, resulting in an excess of pyruvic acid; instead of being oxidized to carbon dioxide and water in the citric acid cycle, pyruvic acid is reduced to lactic acid by the enzyme lactic dehydrogenase. This type of acidosis is usually present when arterial oxygen tension is less than 30 mm.Hg if organ perfusion is impaired, especially in patients who have an associated impairment of liver function (lactic acid is metabolized by the liver).[3]

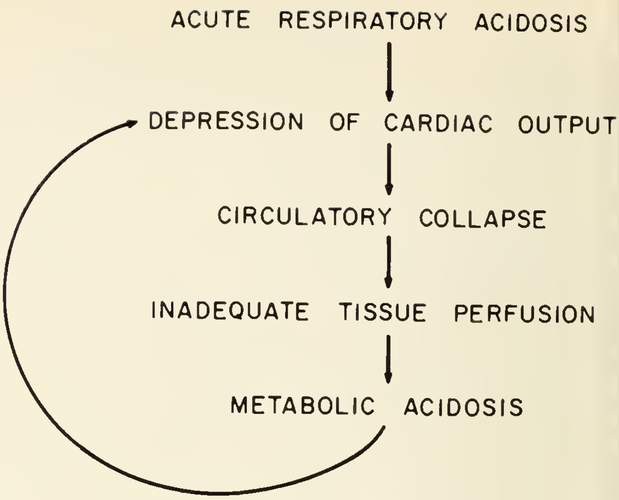
ACUTE RESPIRATORY ACIDOSIS
DEPRESSION OF CARDIAC OUTPUT
CIRCULATORY COLLAPSE
INADEQUATE TISSUE PERFUSION
METABOLIC ACIDOSIS

Figure I

Circulatory and metabolic consequences of acute respiratory failure.

An important consequence of respiratory failure is circulatory collapse due in part to the effect of high arterial carbon dioxide tension and low pH on myocardial muscle (Fig. I). Metabolic acidosis so produced will be superimposed on respiratory acidosis with a further depression of cardiac output as a result. This vicious circle could be broken and even prevented if respiratory failure is relieved.[4]

Summary

Hypoventilation, inequality of ventilation and perfusion, and diminished diffusion may impair the respiratory gas exchange to such a degree that respiratory failure will result. The effects of hypoxia, hypercapnia and acidosis are briefly discussed. Prevention or at least delay in onset of respiratory failure is almost always possible if the mechanisms and early manifestations are recognized in time.

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Humidity And Water Aerosol Therapy

Donald F. Egan, M.D.

■ Water is a major therapeutic agent in the treatment of broncho-pulmonary disease, and with improvement in inhalation therapy equipment and techniques it is being used with increasing efficiency. Unfortunately, the inhalational use of water is associated with many different terms, and it is necessary that some precise definitions be understood and used. Inhaled water falls into two categories, and differentiation must be made between humidity and vapor on the one hand, and mist, aerosol, "cold steam", and fog on the other. In the following discussion, vapor will be used as representative of the first category, and aerosol of the second. *Water vapor* is water in a gaseous form, sometimes referred to as "molecular water", and as such is invisible. The water molecules of vapor mix with the molecules of the other gases of the air, and in a real sense comprise another constituent of air. In this role, water is space-occupying among the other gases, and it exerts its own pressure similar to the partial pressure of its neighbors. However, water vapor pressure (P_{H_2O}) is not dependent upon its fractional concentration in the air, as is the case with the other air gases, but varies directly with the relative amount of vapor present (see relative humidity, below), and the temperature. For example, in air saturated with water vapor at 21°C, the water vapor exerts its own pressure, as a gas, of 18.7 mm Hg, regardless of the barometric pressure, and at body temperature of 37°C this value rises to 47 mm Hg.[1] Although vapor pressure is not a parameter that is measured clinically, it is the kinetic force which determines the direction of water exchange between inhaled gas and the respiratory mucosa.

By definition, an *aerosol* is the suspension of minute particles of liquid or solid in a gas. Thus, aerosolized water is water in a very fine particulate form, down to sub-micronic diameters, held in suspension in the air. The important difference between it and vapor is that a water aerosol is liquid water, not gaseous, and exerts no pressure. Aerosol particles are visible or reveal their presence by light diffraction, thus the terms "mist" and "fog" applied to the therapeutic use of water aerosols. "Cold steam" is a poetic but innacurate reference to the same phenomenon.

The quantitative evaluation of these two forms of water differs. Depending upon circumstances, *water vapor* is usually calibrated according to one of the following three scales:

1. *Absolute Humidity:* This is a measure of the actual weight of water vapor per unit volume of gas, generally as grams of water per cubic meter of gas, or more frequently in physiological use, as milligrams per liter of gas. Tables and formulae are available for calculation of these values.[2]

2. *Relative Humidity:* The ratio of the absolute humidity, or the actual amount of water vapor present at a given temperature, to the vapor capacity, or the amount of water the gas is able to hold at that temperature, is the degree of gas saturation with moisture. Relative humidity must always be referred to a specific temperature.

3. *Percent Body Humidity:* A convenient term for respiratory application,[3] per cent BH refers to the amount of water vapor in a volume of gas, as a per cent of the water in gas saturated at body temperature. For example, 21°C air, saturated with water vapor contains 18.4 mg/liter of water, while saturated air at body temperature contains 43.8 mg/liter. The room air could be said to contain 42 per cent body humidity.

Aerosols are quantitatively classified according to:

1. *Particle Size or Concentration:* Aerosols are most frequently referred to in terms of the mean size of their particles, and the overall range of sizes. Although particle sizes may extend from 100 microns to 0.005 microns, most therapeutic aerosols are in the 10 to 0.1 micron range. Less frequently aerosols are measured as numbers of particles per cubic millimeter of gas.

2. *Minute Volume of Aerosol Aerosolized:* The number of milliliters of water aerosolized per minute is often useful clinically, especially with prolonged use of some of the newer large volume aerosol generators.

It may be suspected that there is overlapping in the therapeutic use of water vapor and aerosol, but it is still convenient to describe their indications separately for clarity, and to emphasize their basic differences. *Water vapor* is used specifically to pre-

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vent or correct "humidity deficit" in the respiratory tract. The normal tracheobronchial tree is able to maintain saturation of inspired gas at body temperature by evaporation from the respiratory mucosa, most of which probably takes place proximal to the carina. This mechanism assures that gas ventilating the pulmonary tissue contains 44 mg of water vapor per liter of gas. When inspired gas contains less than this amount of water, its vapor pressure is less than the 47 mm Hg of body humidity, and the pressure gradient thus established moves vapor from mucosa to gas. A humidity deficit of pathological degree may be produced by two general circumstances.

1. *Breathing Dry Gas:* The administration of therapeutic gases from tank or central supply, subjects the respiratory tract to large volumes of vapor-free gas. The normal humidification process may be inadequate to cope with this load, drawing on the water content of the entire mucosal surface. Such failure will be hastened or aggravated by an associated dehydration incident to systemic disease. Depletion of mucosal moisture leads to an increased viscosity of the "mucus blanket" of the tract, and a slowing of its cephalad movement which is so necessary to maintain good hygeine. Ciliary action is also adversely effected. Increased or abnormal secretions, often present in patients requiring gas therapy, suffer from drying and become less mobile, significantly contributing to airway resistance.

2. *Mucosal Crusting:* Abnormal secretions, the result of bronchopulmonary infections and irritations, or systemic disease, may cover the mucosal surface with a dry or crusted coat. Relatively impervious to the diffusion of moisture, it blocks the normal humidification process and its own dessication is perpetuated by the inhalation of air or therapeutic gas containing less than body humidity.

Water aerosol serves a dual role. Its principal function is to deliver liquid water, in minute particle form, to the mucosal surface. The site of maximum action is determined by many factors, chief among which is particle size, and the resultant depth of penetration into the respiratory tract. The water which "rains out" in the airways is intended to dilute thick secretions or moisten dessicated crusts, for easier removal by cough or aspiration. In addition to the local effect of physical water, the aerosol particles also provide a source of moisture for humidifying the inhaled carrier gas. As the inspired gas enters the warmth of the body and its vapor capacity increases, suspended water particles evaporate into the gas, raising its vapor tension to that of body humidity. Because water aerosol can both wet and humidify, it might seem reasonable to use aerosolized water exclusively. However, there are indications for humidity alone, when the administration of liquid water to the respiratory tract is not only unnecessary but undesirable. Also, in some types of respiratory equipment, the precipitation of suspended water particles in gas tubing is both a nuisance and a hazard.

The instruments used to provide these two types of water therapy are humidifiers and aerosol generators, although there is a considerable overlap between them in both function and application, and they sometimes differ only in degree. It may be generalized, however, that a humidifier is designed to deliver a maximum amount of water vapor with a minimum of particulate water, and an aerosol generator a maximum number of water particles of uniform size which will penetrate the respiratory tract before depositing. Humidifiers frequently produce some aerosol, but the key difference between them and aerosol generators is the tremendous volume of water particles of the latter. Both are available for use with water at room temperature, or by the inclusion of heating devices, with water at elevated temperatures. By raising the water temperature far above that of the body (up to 60°C), humidifiers can add enough vapor to inspired gas so that, despite the drop in temperature in transit from instrument to patient, when the gas enters the body it will be at or near body humidity. Aerosol generators employ the same principle so the carrier gas will have its quota of vapor and will not "steal" it from the suspended particles which are intended for deposition.

The humidifiers and aerosol generators in common use fall into the categories listed in Table I. The jet type of both humidifier and aerosol generator is the most widely used, and employs the venturi principle, illustrated in Figure I. The main difference between a venturi humidifier and aerosol generator lies in the arrangement of baffles, which trap particles in a humidifier, and allow the escape of particles of specific sizes in an aerosol generator. A pass-over humidifier directs the flow of inspired gas across the surface of a reservoir of heated water. The bubble diffusion humidifier carries the gas through a porous diffusion head. This is a historic type of humidifier and is very inadequate, although some newer units employ improved modifications of this principle, with better results. Impeller type aerosol generators use rotating fins to break water into small particles and literally throw

TABLE I.
TYPES OF HUMIDIFIERS AND AEROSOL GENERATORS

Humidifiers	*Aerosol Generators*
Jet	Jet
Pass-over	Impeller
Bubble Diffusion	Ultrasonic

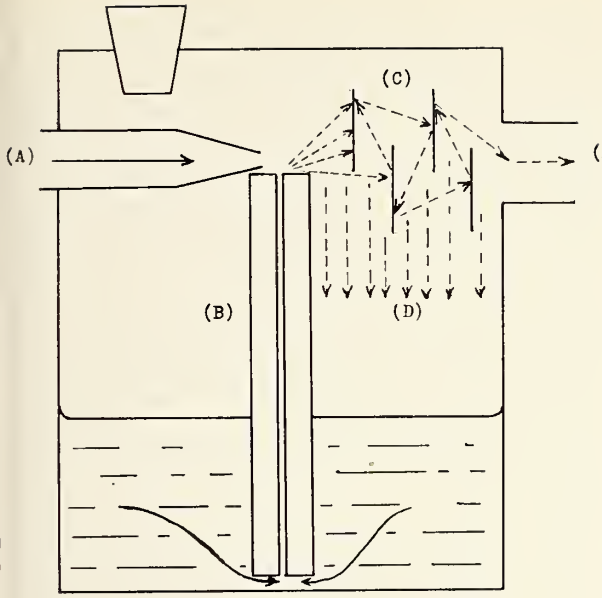

FIGURE I

The Jet or Venturi Principle of Aerosol Generation. A high velocity jet of gas (A) passes across capillary tube immersed in water (B), creating a drop in pressure at upper end of capillary. Water rises in tube and is blown by jet against a baffle system (C) which removes unwanted water particles (D), returning them to reservoir. Outflow gas (E) to patient contains the desired number or size of water particles. For humidification, most of the particulate water is baffled, or evaporates to saturate the outflow gas. For water deposition, the baffles allow the escape of large numbers of particles suitable for airway penetration.

them into the air. If large enough, these can be effective. The newest addition to the group is the ultrasonic aerosol generator which produces the largest volume of water particles, having the potential of aerosolizing up to 6 milliliters of water per minute. High frequency sound waves of 1.3 megacycles per second are transmitted by a ceramic disc to a water reservoir, and break the water into a large volume of particles of a size able to penetrate the lower respiratory tract. The effectiveness of this instrument has made it one of the most useful means of providing both humidity and water aerosol in a wide variety of circumstances.

Ther is no simple formula to guide the selection of one piece of equipment over another, and such non-clinical factors as economics, and availability of personnel to administer and maintain the equipment cannot be ignored. An evaluation of each patient's physiological needs in terms of vapor versus liquid water, and an understanding of the function and potential of available equipment, will give the best assurance of successful therapy.

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Therapeutic Uses Of Helium

Donald F. Egan, M.D.

■ The obstructive element of bronchopulmonary disease is one of the most common causes of respiratory disability, and most difficult to relieve. At its worse during an acute exacerbation of a chronic process, obstruction may show little response to measures earlier effective. Frequently overlooked in the treatment plan is helium, which possesses properties that make it one of the most useful agents in overcoming obstruction. Probably unfamiliarity with its potential, coupled with apprehension towards the use of a strange, non-physiological gas, is responsible for its absence among the facilities of many community hospitals. The characteristics of helium will be described, and indications for, and techniques of its use discussed.

Before concentrating on the use of specific therapy, a brief review of relevant pathophysiology is indicated. As a general statement it may be said that the obstruction of bronchopulmonary disease is the result of mucosal edema, bronchospasm or increased bronchial secretions. While it is obvious that therapy must be directed towards the correction of these defects, this takes time, and meanwhile symptomatic supportive measures are essential. The persistence of prolonged diffuse airway

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obstruction imposes upon the patient a tremendous work load. To create a negative intrathoracic pressure, suitable to insure adequate pulmonary ventilation in the presence of obstruction, the patient must utilize his accessory ventilatory muscles. Even with great effort, the result is usually a poorly distributed ventilation, and increasing fatigue will often lead to ventilatory failure with hypoxia and subsequent hypercapnea.

The resistance to flow through airways, normal or diseased, is related to two physical characteristics of the gas being moved—*viscosity* and *density*. In the presence of a relatively smooth conducting tube, where gas flow is mostly linear or *laminar*, the viscosity of a gas is a major determinant of its flow. Briefly, viscosity is a measure of the frictional resistance to forward motion among the gas molecules, and between the molecules and the wall of the conducting tube. One of the laws of fluid physics (Poiseuille's Law) explains that for a gas with a given viscosity, at a constant pressure, the flowrate of the gas varies directly with the 4th power of the tube radius. Or, to view it slightly differently, at a constant flowrate, the pressure drop along the tube varies inversely with the 4th power of the radius. This concept explains why, in normal or diseased bronchi, there is a drop in pressure as a volume of gas moves through ever narrowing airways. However, among the gas mixtures used to ventilate the lung, the actual differences in their viscosities (measured in micropoises) is not significantly great to make this parameter of practical use in choosing a suitable gas, even to compensate for severe obstruction.

The pattern of flow through a passage which is tortuous, frequently dividing, or obstructed with sudden abrupt narrowing, is described as *turbulent*. There is much eddy formation and acute deflections of the flow, as is seen in the bed of a rock-strewn stream. In this circumstance, the most influential property of a moving gas is its *density*. It is recalled that density is a weight per volume relationship, and in gases it is the ratio between the gram molecular weight of gases and the volumes occupied by the gram molecular weights. Since gram molecular weights of all gases occupy 22.4 liters, gas densities are calculated by dividing their gram molecular weights by 22.4, and expressing the densities in grams per liter. Also, since the value of 22.4 liters is common to all gases, it is evident that, for comparative purposes, densities of gases are related to one another as are their gram molecular weights. Although it should be intuitively evident that the less dense a gas, the easier it can by-pass an obstruction, the reason can be better understood if it is pursued a bit further by viewing the physical phenomena from two slightly different points.

First it should be noted that as a flow of gas passes from a relatively wide passage into one which is relatively narrow, if the driving force is constant, the gas velocity must increase to maintain the same volume leaving as entering the restriction. Bernouilli's principle demonstrates that as the velocity of a gas increases, the pressure it exerts decreases, and there is thus a pressure drop across an obstruction. However, since less driving pressure is required to move a light gas (low density) than a heavy one, at the same velocity there would be less of a pressure drop. In ventilation this would mean greater efficiency and less work expenditure in breathing.

Second, the movement of a gas through the narrow aperture of an obstruction subjects it to some of the principles of *diffusion,* or the passage of a gas across an obstruction in response to a pressure gradient. The rate of diffusion of a gas is described by Graham's Law as being inversely proportional to the square root of the density of the gas. Again, as indicated above, comparative rates of diffusion of two gases can be described as inverse proportions of the square roots of their gram molecular weights.

At the present, helium is the only low density gas acceptable for medical use. With a density of 0.179 grams per liter, it is second only to the highly inflammable hydrogen as the lightest of gases. Chemically, and thus physiologically, helium is an inert element neither participating in nor interfering with any biochemical process. It is odorless, tasteless, non-combustable, non-explosive, poorly soluble, and a good conductor of heat, sound, and electricity. Since helium cannot support life, it must be used as a helium/oxygen mixture. Any combination that provides a minimum of 20 per cent oxygen is possible, but it must be born in mind that as the percentage of helium in the mixture decreases, the low density property which is the only indication for its use, also decreases. Table I lists the densities of some commonly used therapeutic gas mixtures, and comparative diffusibility of several pairs of these gases. Although pure oxygen and pure helium can be mixed at the bedside, it is much safer to employ tanks of pre-mixed gases, prepared commercially. Two commonly used mixtures are 80 per cent helium with 20 per cent oxygen, and 70 per cent helium with 30 per cent oxygen. The former is essentially air, with helium substituted for nitrogen, and the latter provides a therapeutically useful excess of oxygen at only a slight cost in density loss.

Table I

Densities and Relative Diffusion Rates of Selected Gases (Rate of Diffusion Varies *Inversely* With Square Root of Density)

Gas	*Percentage*	*Density*	$\sqrt{\textit{Density}}$	*Relative Diffusibility*
Helium	100	0.179	0.423	
Air	100	1.293	1.135	
Oxygen	100	1.429	1.182	
Oxygen/Nitrogen	40/60	1.321	1.105	
Helium/Oxygen	80/20	0.429	0.655	
Helium/Oxygen	70/30	0.554	0.745	
Oxygen	100	⤨	1.135	0.960
Air	100		1.182	
Oxygen/Nitrogen	40/60		1.135	1.027
Air	100		1.105	
Helium/Oxygen	80/20		1.135	1.743
Air	100		0.655	
Helium/Oxygen	80/20		1.182	1.805
Oxygen	100		0.655	
Helium/Oxygen	70/30		1.182	1.586
Oxygen	100		0.745	

Because helium itself presents no hazards, very few precautions are necessary as long as an adequate oxygen supply is provided. The following points of technique should be noted however:

1. Helium mixtures must always be given in a tightly closed system. Because of their high diffusibility, the gases will readily escape from any leak. Tents and catheters are not satisfactory, and such mixtures are most conveniently administered by a tightly fitted mask with a non-rebreathing bag, or through a cuffed endotracheal or tracheotomy tube. They are very advantageously given by intermittent positive pressure ventilators.

2. Most hospitals use gas flowmeters which are calibrated for oxygen, and since these employ some type of a float to record the liter flow, gauge readings will not be accurate for the lighter helium/oxygen mixtures. Special meters are available, but are not necessary, as correction can be made for the helium gases. Table I shows that an 80/20 He/O_2 mixture is 1.8 times as diffusible as 100 per cent O_2, and a 70/30 He/O_2 mixture is 1.6 times as diffusible. Thus, the gauge reading must be adjusted to record the *desired* liter flow per minute *divided* by either 1.8 or 1.6, depending upon the gas used. Factors for any other combination can be calculated.

3. The low density of helium mixtures make them poor vehicles for the transport of aerosol particles. Humidifiers, of course, should be used, but therapeutic concentrations of particles of water or pharmaceuticals cannot be expected.

4. The only side effect directly attributable to helium is a benign one, but one which should be kept in mind. The spoken voice is badly distorted at a pitch so high as to make it almost unintelligible. This is of importance only in the conscious patient who should be warned of this phenomenon, and reassured that it will disappear within a few seconds of discontinuance of therapy.

In summary, the indications for, and rationale of the use of helium-oxygen mixtures are discussed. If not responsive to the usual measures, patients with persistent and diffuse airway obstruction may be afforded relief from their struggle to ventilate before exhaustive failure depletes their energy reserve.

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Acute Necrotizing Pneumonia

Stephen B. Sulavik, M.D.

■ We have recently had occasion to review several cases of acute fulminating necrotizing pneumonia in previously non-hospitalized patients. The clinical and roentgen picture have shown considerable similarities although the specific responsible organism varied. These similarities include an acute toxic state with or without systemic shock, scant productive cough, temperature elevation, auscultatory evidence of pneumonia and a chest X-ray pattern demonstrating areas of rarefaction in the areas of pneumonic consolidation (highlighting). The extreme severity of such a situation and the need for prompt and as specific treatment as is possible cannot be overstated. (Figures I and II). It is the purpose of this paper to relate some thoughts pertaining to initial diagnosis and early management in this particular clinical setting.

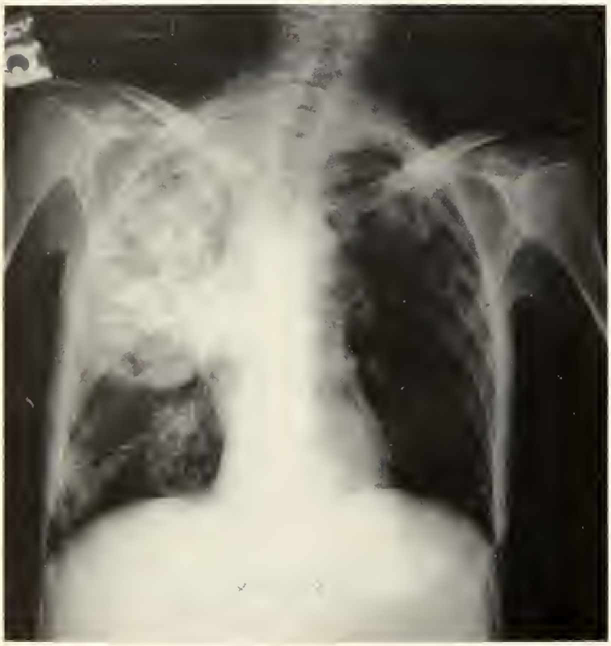

Figure I

50 year old female. Prominent "highlighting." Death occurred within 5 hours of hospital admission. Autopsy revealed acute tuberculous pneumonia.

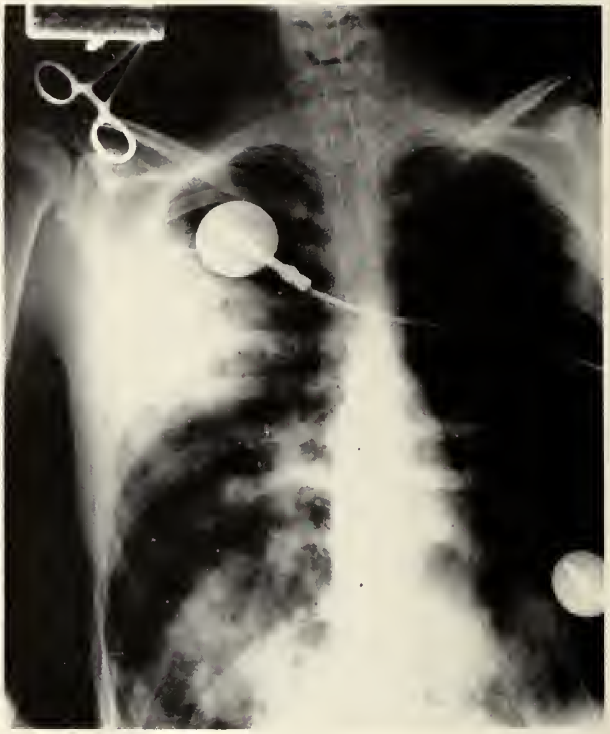

Figure II

20 year old female with mild asthma. Prominent "highlighting." Death occurred within 15 hours after admission. Gram stain of sputum revealed only gram positive diplococci. Culture of lung grew 4+ hemolytic staphylococcus aureus.

Early recognition of this type of pneumonia is extremely important because of its severity, high mortality, tendency to cause chronic pulmonary disability and failure of certain of the causative organisms to respond to penicillin. Those bacteria capable of producing acute necrotizing pneumonia include the hemolytic staphylococcus aureus, klebsiella pneumoniae, Type III, pneumococcus, alpha and beta hemolytic streptococcus and the tubercle bacillus. Most commonly, however, the offending organism is found to be the hemolytic staphylococcus aureus or klebsiella pneumoniae and occasionally the Type III. pneumococcus. Though a history of chronic alcoholism, diabetes mellitus, underlying chronic debilitating disease in a patient with pneumonia should alert one to the possibility of a necrotizing lung process, such a history may often be absent. (Figures I-V). The clinical signs and symptoms, degree of temperature elevation and white blood cell count often help to define the severity of the situation but contribute little with

From the Section of Chest Diseases, Department of Internal Medicine, Yale-New Haven Medical Center.

DR. STEPHEN B. SULAVIK, Assistant Professor of Medicine, Director, Winchester Chest Clinics.

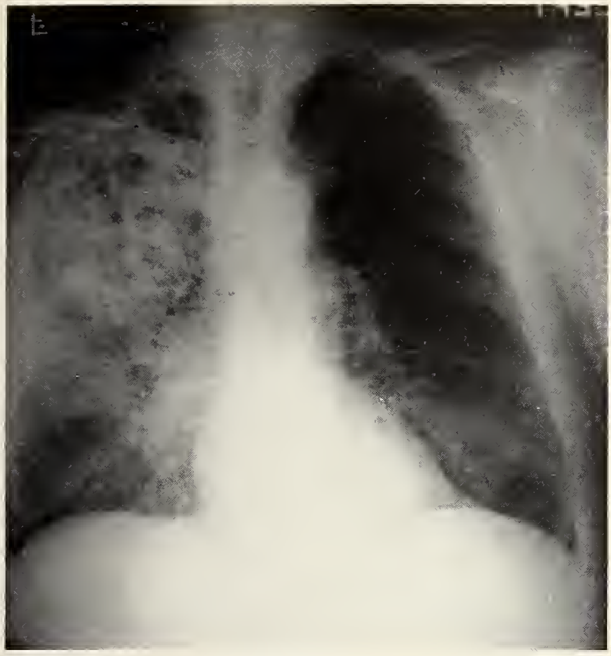

Figure III
Staphylococcal pneumonia with marked "highlighting" in an elderly male.

respect to the specific bacterial cause. The following are some diagnostic and therapeutic considerations which may be of value.

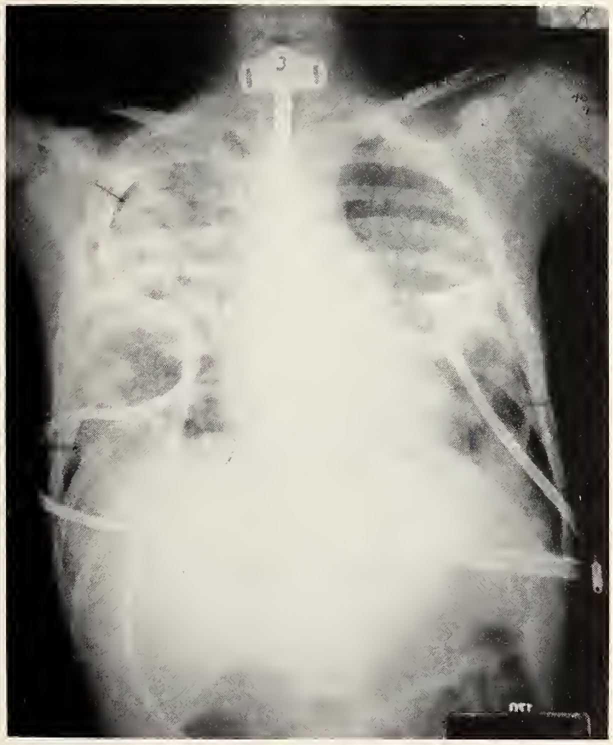

Figure IV
14 year old male. Staphylococcal pneumonia with complications of bilateral pneumothorax. "Highlighting" is prominent.

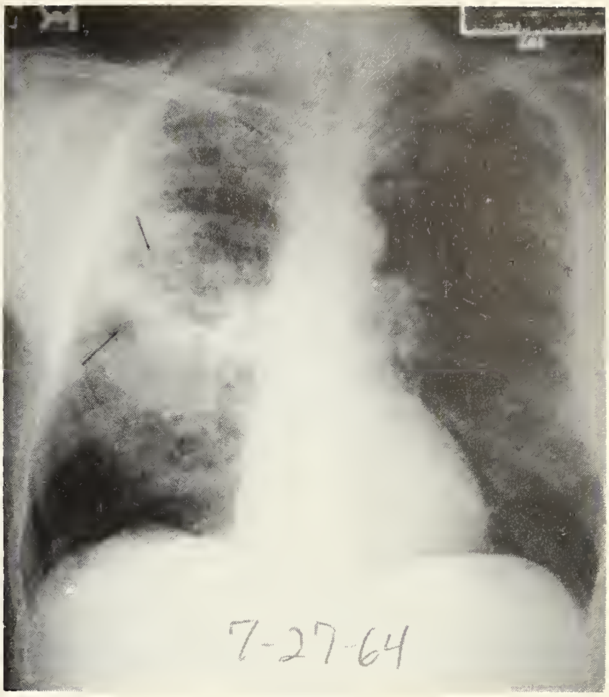

Figure V
Male, age 59. Gram positive diplococci only were seen on sputum smear. Culture of sputum grew 4+ Klebsiella.

Some Diagnostic Considerations

I. THE CHEST ROENTGENOGRAM

A most important initial clue may be found in the chest x-ray. The finding of areas of rarefaction or frank multiple abscesses in the area of consolidation (highlighting), (Figures I-VI), should immediately suggest a necrotizing lung process. The absence of such roentgen findings, however, in no way rules against the diagnosis of a necrotizing process since necrotization is merely a later stage of an initial lobar or pseudo-lobar consolidation. Primary diagnostic considerations, then, when highlighting is evident, are those of staphylococcal or klebsiella infection. Commonly, highlighting is the *only* clinical evidence suggestive of a necrotizing process. Other x-ray findings which may be of value include: (a) an associated pneumothorax, (Figure IV), or pneumatocele, (suggestive of staphylococcal infection); (b) bulging of the major or minor fissure, (Figure VI), (in itself indicating only that an obstructing pneumonia is present) which is observed in approximately 15 per cent of pneumonias due to the klebsiella pneumoniae.

II. THE GRAM STAIN AND CULTURE OF THE SPUTUM

The finding of a marked predominance of Gram negative organisms or acid-fast bacilli may be of considerable help in the initial diagnosis and therefore therapy. However, in Gram negative infections, not uncommonly there is failure to find Gram negative organisms even on careful search,

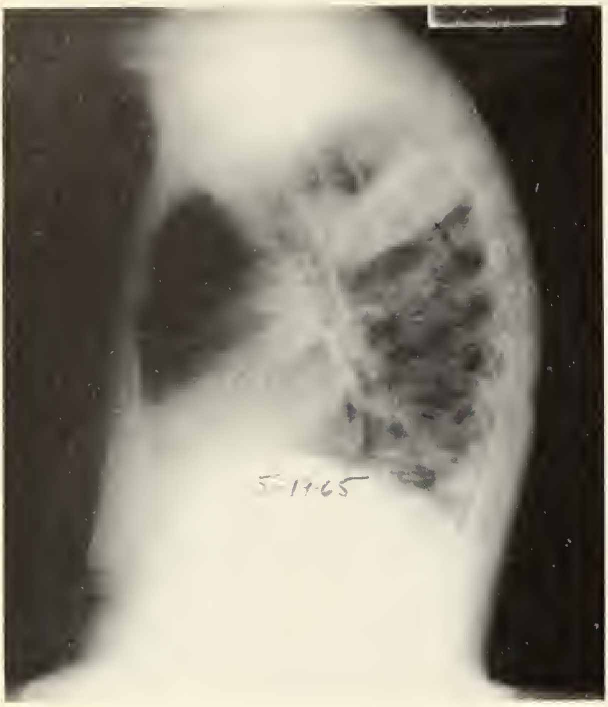

FIGURE VI

77 year old, female, diabetic. Lateral view demonstrating "highlighting" and bulging fissure. Gram positive diplococci only were seen on sputum smear. Klebsiella was cultured repeatedly from the sputum.

(Figure V-VI), and since considerable numbers of Gram positive organisms may also be seen in the same smear, Gram negative organisms may be overlooked. The finding of Gram positive organisms only may be less helpful because of the difficulty in: (a) properly distinguishing the various organisms, (Figure II), and (b) the difficulty in assigning relative diagnostic importance to mixtures of these Gram positive flora even if properly identified.

A very important consideration, too, is that the coughed sputum specimen may not represent the actual offending bacterial flora which lies deep in the respiratory tract. Transtracheal aspiration[1], in an effort to obtain an adequate lower respiratory tract specimen for smear and culture, if there is scant or no sputum being raised or if there is any doubt with respect to the responsible organism in the initial sputum smear, should therefore be employed.

Some Therapeutic Considerations

I. ANTIBIOTICS

Initial antibiotic treatment of the patient presenting the clinical picture described should be directed at "broad" coverage with particular reference to the staphylococcus, klebsiella and pneumococcus. This 24 to 36 hour antibiotic regimen, maintained only until specific cultural data with sensitivities is obtained, might include such a combination of drugs as cephalothin, streptomycin and isonicotinic acid hydrazide (INH). This would also cover the possibility of Mycobacterium tuberculosis. Several other drug combinations certainly are possible.

II. ABNORMALITIES OF PULMONARY GAS EXCHANGE

Abnormalities of pulmonary function and gas exchange have not been studied in detail in the acute phase of pneumonia primarily because of the serious nature of the clinical situation. Arterial oxygen desaturation, however, is often quite prominent and if allowed to become extreme may result in cardiac arrest. Hypoxia is the result of pulmonary arterial perfusion of distal air spaces which are not ventilated due to their congestion with pneumonic exudate, partial obstruction or frank collapse.[2] Oxygen desaturated pulmonary arterial blood, therefore, unable to receive oxygen from these non-ventilated air spaces, mixes with oxygen saturated pulmonary venous blood coming from remaining well ventilated lung areas and results in admixture of oxygenated and non-oxygenated blood (venous admixture). It is obvious: (a) that an intense program must be carried out in an effort to "unplug" areas of non-ventilated lung, (bronchial drainage) in order to facilitate adequate gas exchange and (b) that the patient's arterial oxygen saturation be maintained at an adequate level. Since high concentrations of inspired oxygen, (producing a high alveolar oxygen tension) over a period of time may cause atelectasis[3] and further compound the problem, one must carefully keep the inspired oxygen concentration at the lowest level which will maintain an adequate arterial oxygen tension, (e.g. above 60-70 millimeters of mercury) thus maintaining an adequate arterial oxygen saturation. Repeated determinations of the arterial tension, therefore, are necessary.

The carbon dioxide tension is generally normal or low in acute pneumonia as a result of alveolar hyperventilation which follows the reduction in arterial O_2 tension. However, in patients with underlying lung disease, (e.g., chronic bronchitis, emphysema), a significant degree of carbon dioxide retention may occur. Evaluation of the arterial carbon dioxide tension will alert one to this type of ventilatory failure.

To best provide adequate bronchial drainage, effective distribution of mucolytic and bronchodilator aerosols, and maintain proper alveolar ventilation, tracheostomy with intermittent positive pressure breathing, (IPPB) will most often be employed.

Arterial pH determinations are also important since: (a) severe hypoxia may result in metabolic acidosis, particularly if shock has occurred; (b) if too vigorous mechanical ventilation is applied, alveolar hyperventilation with resulting respiratory alkalosis may occur, and (c) should the carbon dioxide tension rise, respiratory acidosis may ensue. Adequate detection of these changes is possible only by obtaining serial arterial blood gases and pH. Careful monitoring of the arterial blood gases, attention to the inspired oxygen concentration and rational adjustments of the IPPB apparatus, based upon the results of the arterial blood gases, should result in significant improvement of these ventilatory disturbances.

Summary

The following aspects of acute necrotizing pneumonia have been briefly discussed and may be of value in the initial diagnosis and management.

1. "Highlighting" observed on the chest x-ray should suggest the diagnosis of a necrotizing lung process. The absence of "highlighting" does not, however, rule against this diagnosis.
2. Initial "broad" antibiotic coverage for those organisms known to produce a necrotizing process is suggested.
3. The initial Gram stain of the sputum may be misleading and should any doubt exist in this regard transtracheal aspiration for smear and culture should be employed.
4. Prompt attention should be given to the problem of hypoxia which commonly occurs.
5. Constant awareness of metabolic and ventilatory complications.
6. The importance of serial arterial blood gases and pH determinations in initial therapy and management.

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3. Nash, Gerald, Blennerhassett, John B., and Pontoppidan, Henning: Pulmonary lesions associated with oxygen therapy and artificial ventilation. New Eng. J. Med., 276: 368-374, 1967.

Personal Physician

Never has the time been more propitious and the need greater for the reconstitution of the personal physician. With the increasing plethora of specialists, and the ever growing quantity and complexity of new knowledge that must be sifted and evaluated by an authoritative central source, direction and coordination of the patient's course to restored health is presently the most important function in medicine. And, at the present rate of progress, this function can only continue to grow in importance. The patient needs an expert pilot to steer him through the maze of specialists and subspecialists; to critically review and judge the pronouncements of the specialists; to see the illness in its entirety vis-à-vis the total patient; to make the important decisions; to show comforting concern for him; to assume the final responsibility; and to be *his* personal physician. —Zale Yanof, M.D.

E. TREMAIN BRADLEY, M.D.

Born: Nyack, New York, 1909.

Education: Riverdale Country School, N.Y.C. and Phillips Exeter Academy, Exeter, N.H.—graduated 1927. Princeton University—A.B. Class of 1931. Cornell University Medical School—M.D. 1936. Taught English at Hotchkiss School, Lakeville, Conn.—1931-32.

Training: Rotating internship Union Memorial Hospital, Baltimore from July 1936 to June 1937; Surgical pathology under Drs. A. P. Stout, V. Franz, and C. Haagensen July 1937 to December 1937; Surgical residency Roosevelt Hospital—January 1938 to September 1940; House officer at Boston Lying-In October 1940 to May 1941.

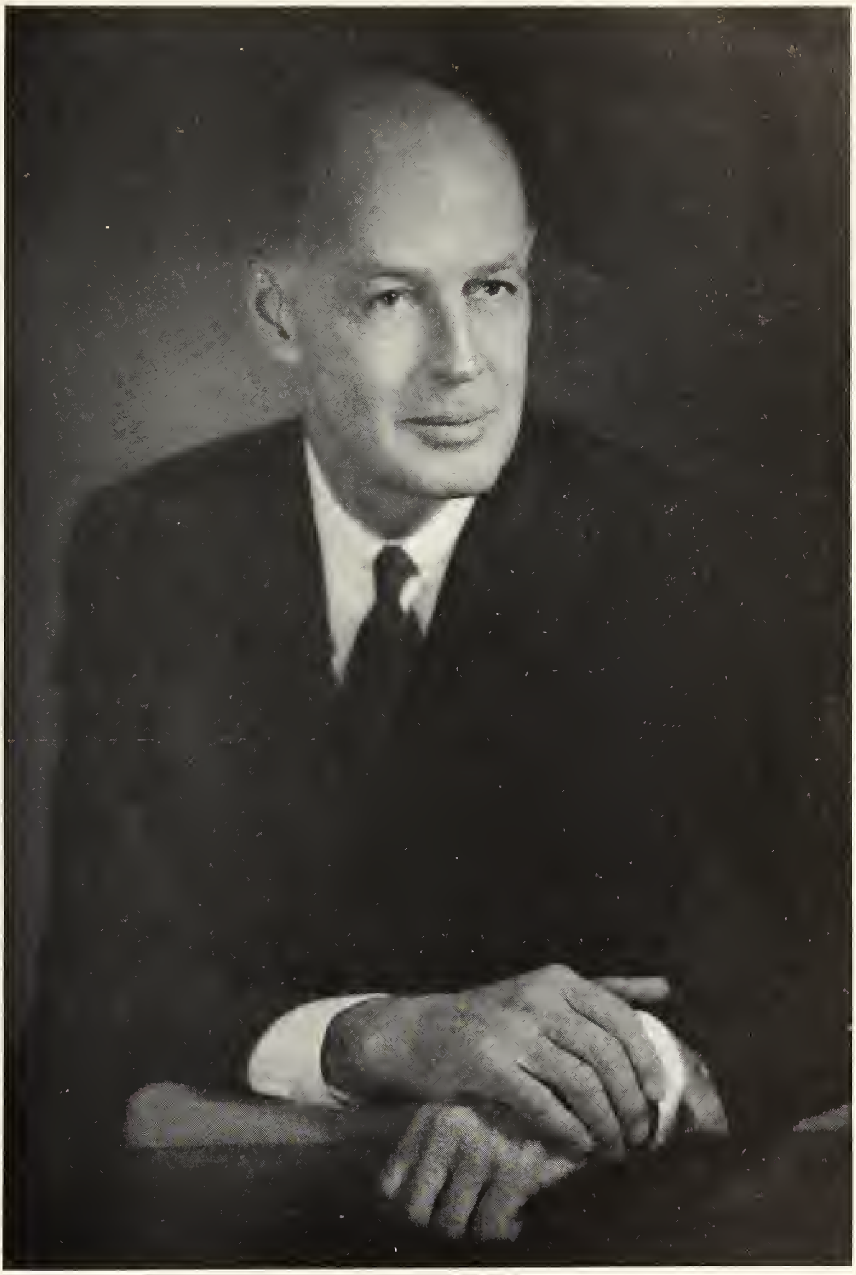
Military Service: Entered active service May 1944, served as Assistant Chief of General Surgical Section and General Surgical Consultant for the 3000 bed Cushing General Hospital until discharged September 1946 with rank of Captain.

Practice: Consisted of surgery, gynecology and obstetrics in New Canaan, Connecticut from May 1941 to May 1944. On resuming practice in 1946, obstetrics was eliminated.

Hospital Appointments: At Norwalk Hospital — Attending in General Surgery, in Neoplastic Diseases, in Thoracic and Cardiovascular Surgery. Director of Department of Neoplastic Diseases. At St. Joseph's Hospital in Stamford and at Roosevelt Hospital in New York City—Courtesy Staff in Surgery. Fellow of the American College of Surgeons.

Community Activities: Served on the Board of Directors of the New Canaan County School, the Red Cross, the Visiting Nurse Association, and the Cancer Society. Was President of the Norwalk Cancer Society and serves on the Executive Committee still. Member of the Country Club of New Canaan and of the Princeton Club of New York.

Medical Society Activities: Fairfield County Medical Association—member of Public Relations Committee and Delegate to the House—five years; Chairman of Public Relations Committee of the Connecticut State Society—four years; Councilor from Fairfield County Medical Association 1960-65; Vice-President of Connecticut State Medical Society 1965-66; President-Elect 1966-67.



E. Tremain Bradley, M.D.
President

THE PRESIDENT'S PAGE

The gyrations of the mind and the outpourings of the heart do not flow easily from my tongue or pen, yet this page presents a welcome challenge. Here is an opportunity to communicate with all members of the Society.

Participating in deliberations of the Council over the past seven years has been a maturing experience. Each Councilor, having carefully studied in advance the vast quantity of "background material", has drawn an honest and logical conclusion. Yet these finalities may be as disparate as the angles of a triangle. Only when these preconceptions are relegated to the background can the facts be brought together—sand from there, cement from here, water from up there and bricks from down below—to build the best possible architectural structure—to reach nearer the truth. We have communicated effectively.

But that's only in the Council. With the rapid advancement of medical science and the development of specialties and subspecialties, a variety of organizations—Colleges, Academies, Societies—have been created for the interchange of technical information, the stimulation of thought and the appraisal of experience. Each group is inspired to enhance the method of practice and the care of the public. It is more than conceivable that parts of these worthy projects may seem in conflict. Yet if handled in the light of other activities and circumstances, the rough edges of each could be made to dovetail with the others. The Connecticut State Medical Society is our only all-inclusive medium, where all the specialties and "non-specialties" are united. Nothing will weaken the system of private practice as quickly as disunity. It therefore behooves us to communicate freely—and early—the thoughts and proposed actions of the sundry groups, with the Society as a sort of clearing house. Let's worry less about who "gets credit" for the idea; let's try to make it maximally effective. Even the scheduling of meetings, both scientific and administrative, might well be coordinated on a master list at 160 St. Ronan Street to help avoid conflicts.

The revised format this year for the House of Delegates was designed to improve communication between the membership and those in whom is vested "the superintendence and management" of the Society. First, the component County Associations are urged to transmit their thoughts in resolution form, and Boards of Trustees or Governors can stimulate this. Even an individual can submit a resolution through a Delegate. Then, between the two sessions of the House all reports and resolutions are discussed in Reference Committee. *All* members may request information and express their views in these hearings. After careful consideration of the testimony, the Reference Committee makes its recommendation to the House, where final action is taken.

To better integrate the scientific and the administrative activities of the Society, the next Annual Meeting of the House of Delegates is expected to run concurrently with the scientific session. The general membership can then readily stop in at a Reference Committee without making a special trip. The constituency can confer with the delegates before final action is taken. The resultant proceedings of the House should be more deliberate, less impulsive. You and your representatives will be better informed. Through communication this will become truly *your* Society—and a better Society.

E. Tremain Bradley, m.d.

FROM THE GENERAL MANAGER'S OFFICE

William R. Richards, m.d., *General Manager*
160 St. Ronan Street, New Haven, Conn.
Telephone 865 0587

Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

SUMMARY OF ACTIONS COUNCIL MEETING

Wednesday, March 15, 1967

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Hess, Bradley, Gardner, Brandon, H. Caplan, Fabro, M. Caplan, Polivy, Rogol, Grendon, Egan, Abbot, Spitz, Hastings, Shepard, Cramer, Grant, Pelz, Wilson and Roch. Also present were: Mrs. Lindquist, Mr. Villano, Mr. Chilcoat (AMA) and Dr. Richards. Absent were: Drs. W. Martin, Goldberg, Ayres, Nolan, Ciccarelli, Petrie and Palomba.

II. Routine Business

Life Memberships

It was VOTED to approve applications for Life Membership received from the following eligible Active Members:

Clement F. Batelli, New Haven (NHCMA)
Abe S. Brown, Waterbury (NHCMA)
Nathan A. Goldstein, Branford (NHCMA)
Louis H. Nahum, New Haven (NHCMA)
Emily M. Pierson, Cromwell (MCMA)

Appointment Of Representative—AMA Conference On Nursing

It was VOTED to direct the Chairman to appoint a member of the Society to attend an AMA Conference on Nursing, Chicago, October 6, 1967 as a CSMS representative, and to file a report with the Council on the proceedings thereof. The AMA will reimburse the representative for usual expenses incurred by his attendance. Dr. Martin made the appointment as follows: J. Alfred Fabro, Torrington.

Reports—Council's Fiscal Advisory Committee

It was VOTED to approve reports and recommendations of the Fiscal Advisory Committee as follows:

(a) That $250 be allocated to the budget of the Committee on Accident Prevention, to be used to cover the costs of planning and conducting a Conference on Sports Injuries, Wilbur Cross High School, New Haven, April 22, 1967.

(b) That the Society *not* become an organizational member of the Connecticut State Chamber of Commerce, Inc. at the present time.

(c) That up to $250 be made available to the Conference Committee with the Connecticut Bar Association, as an added allocation to its 1967 budget, to cover operating expenses for the balance of the current fiscal year.

(d) That the sum of $300 be allocated to the printing budget of the Public Relations Department, for the purpose of publishing a "Delegates Manual" for distribution to the present and future members of the CSMS House of Delegates.

Co-Sponsorship Of Seminar On Hospital Emergency Preparedness

At the request of State Health Commissioner Franklin M. Foote, it was VOTED to have the Society join the State Health Department, the Connecticut Hospital Association, the Connecticut Nurses Association and the U. S. Public Health Service in co-sponsoring this Seminar, to be held on May 25 at Valle's Steak House, Hartford. It is understood that John Shoukimas, Hartford, Chairman of the CSMS Committee on Disaster Medical Care, will participate in the program of the Seminar.

Date Of Next Meeting

The date of the next meeting was set for Thursday, April 20, 1967. Starting time is to be 1:00 P.M. (instead of the usual 2:00 P.M.).

III. Old, New And Special Business

Report—Committee On Relative Value Study

It was VOTED to accept as information a report filed by this Committee on progress being made toward obtaining from the various sections and groups participating in the original study recommended changes in the unit values assigned to any of the procedures falling within the purview of those sections and groups. In addition, the report recommended that if a definitive updating of the Relative Value Schedule was to be undertaken, the Council should appoint a small "working committee," having adequate staff and clerical personnel at its disposal, to carry out the project. It is felt that the RVS Committee, as presently constituted and functioning, is not properly equipped to do the job in a satisfactory manner. It was further VOTED to refer this report to the Committee on Third Party Payments for study, report, and recommendations as to the composition and *modus*

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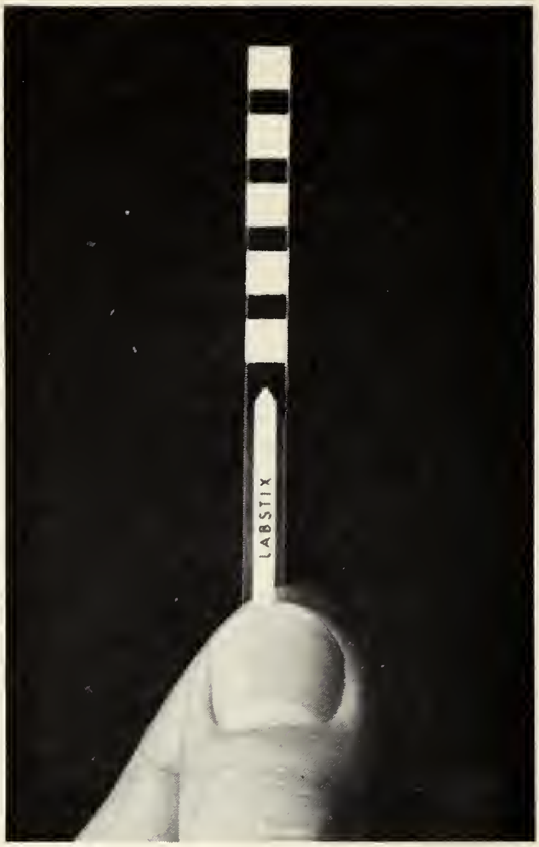

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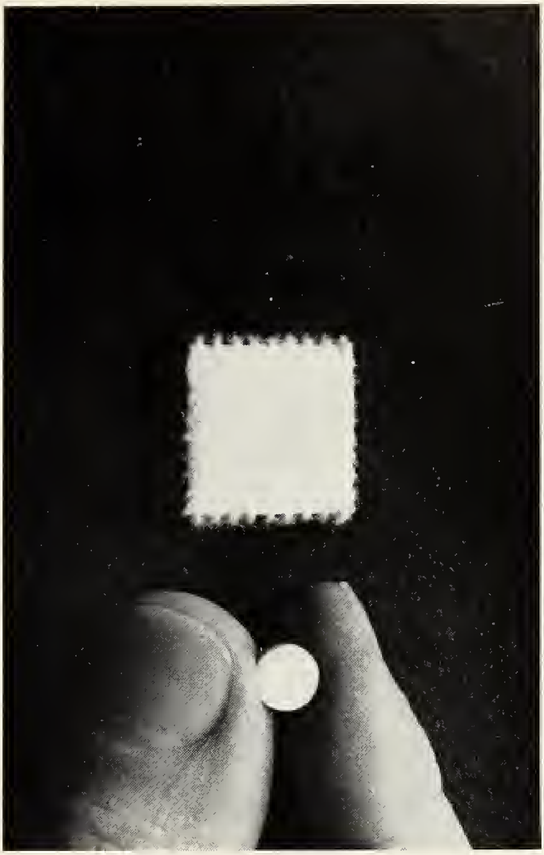

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1. Schleif, R.H.: J.A.PH.A., 46:179,1957 *U.S. Pat. No. 3,062,714

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operandi of the "working committee" suggested by the RVS Committee.

The 1968 Annual Meeting

Although it is possible that changes in the annual meeting format now under study may eventually enable the Society to hold the meetings in facilities less comprehensive than the Hartford-Hilton Hotel, it was VOTED to approve the Hartford-Hilton, Hartford, as the site of the 1968 meeting of the House of Delegates and Scientific Assembly, and to authorize the staff to request the hotel's management to reserve the dates of April 30, May 1 and May 2, 1968, for this purpose.

Appointment Of Representative To State Agencies

In response to a request received from the Commissioner of Health, it was VOTED to recommend Orvan W. Hess, New Haven, as a CSMS representative to serve with the Advisory Committee to the State Department of Health on the implementation of P.L. 89-749, the "Comprehensive Health Planning and Public Health Service Amendments of 1966."

It was further VOTED to accept the resignation of Dr. Hess as a CSMS representative on the Advisory Committee to the State Welfare Department on the Title XIX Program of Medical Assistance, and to recommend to the Welfare Commissioner the appointment of E. Tremain Bradley, Norwalk, to replace Dr. Hess and the appointment of Sidney L. Cramer, Hartford, to serve as Dr. Bradley's alternate.

CSMS Position On HB-3821, 1967 General Assembly

It was VOTED to accept the report of the CSMS Committee on Cooperation with the Medical Schools in Connecticut, which recommend that the Society oppose HB-3821 and similar bills and stating the reasons for this recommendation. The legislative proposal, introduced at the request of the Connecticut Chapter of the American Academy of General Practice, calls for the appointment of a "study committee" by the General Assembly to "study the need for more family physicians in Connecticut communities and to examine what steps the University of Connecticut Medical School is taking to fulfill this need"; "to examine (among other things) the proposed programs of the University of Connecticut Medical School to motivate medical school students toward family practice in Connecticut communities"; and "to report its findings to the Governor and the General Assembly no later than February 15, 1969." The composition of the committee would be: Three members of the State Senate, appointed by the President Pro Tem; three members of the House of Representatives, appointed by the Speaker; and (appointed by the Governor) one member from the CSMS Section on General Practice, one from the Connecticut Academy of General Practice, one from the State Department of Health, and one medical educator.

After full discussion of the report of the Committee on Cooperation, and information on the subject bills furnished by others, the Council VOTED unanimously to adopt the following motion:

"It Is Moved: That the Council of the Connecticut State Medical Society reaffirm the Society's encouragement of the University of Connecticut Medical School to develop a curriculum that includes courses which would lead to the training of future family practitioners for the State; and it is further

Moved: That the Council disapprove and oppose pending legislative bills (HB-3821, HB-3923, and SB-1062) which seek to create a special study committee to oversee the development of such a curriculum at the University of Connecticut Medical School, because of their restrictive natures; and it is further

Moved: That the Council express full confidence in the awareness and ability of the Trustees and Faculty of the University of Connecticut Medical School to develop a curriculum designed to meet the professional health care needs of the State; and it is further

Moved: That notice of these actions of the Council be sent to the Dean of the University of Connecticut Medical School and to the President of the Connecticut Chapter of the American Academy of General Practice."

Discussion—Admission Of Gynecological Patients To Maternity Units

Pursuant to a Council-approved (1964) document titled: "Criteria and Specifications Regarding Participation in the Pilot Program of Admission of Clean Gynecological Patients to Maternity Units," J. Alfred Fabro, Torrington, raised certain questions which may be summarized as follows:

(a) Is this program still in the "pilot" phase, or is it now generally established in hospitals throughout the State? If the latter, to what exent?

(b) Is there a valid scientific reason for limiting such admissions to "clean gynecological cases," and excluding "clean" female surgical cases of other types?

(c) Is there a valid scientific reason for restricting the admission of such cases only to "physicians who are recognized by training and experience as specialists in obstetrics and gynecology," and excluding general surgeons who have been well-trained in gynecology and have full gynecological privileges in other units of the same hospitals?

(d) Does the Joint Commission on Accreditation of Hospitals have any policies that support or are

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The long-continued action of Novahistine LP should help you both get a good night's sleep. Two tablets in the morning and two in the evening will usually provide round-the-clock relief by helping clear congested air passages for freer breathing. Novahistine LP also helps restore normal mucus secretion and ciliary activity—normal physiologic defenses against infection of the respiratory tract. Use cautiously in individuals with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution ambulatory patients that drowsiness may result. Each Novahistine LP tablet contains: phenylephrine hydrochloride, 25 mg., and chlorpheniramine maleate, 4 mg.

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contrary to the provisions of the subject document?

A letter on these matters from Stewart J. Petrie, Derby, was also presented in connection with some of the questions raised by Dr. Fabro.

Following considerable discussion, it was VOTED to refer these and related questions to the Committee on Maternal Morbidity and Mortality (which recommended that the Council approve approve the subject document in 1964) for study and comprehensive "status" report on the program; i.e., scope, experience, findings, conclusions, etc.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on March 15, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT WANTED

INTERNIST—33 years of age, Board eligible, military obligations completed. Wishes to practice with a group in a medium to small community.

SURGEON—31 years of age, Board eligible, military obligations completed. Interested in a practice of general and/or thoracic and peripheral vascular surgery with a group or an associate. Native of Connecticut.

INTERNIST—36 years of age, Board eligible, military obligations completed. Would like to practice with a group, associate or in an institution. Sub-specialty training in Gastroenterology.

INTERNIST—31 years of age, Board eligible, military obligations completed with USPHS. Is looking for a practice in a medium-sized community with a group or an associate, with a sub-specialty in Cardiology.

OPHTHALMOLOGIST—42 years of age, Board eligible, wishes to practice with a group or an associate. Has had experience and training in anesthesiology.

ORTHOPEDIC SURGEON—33 years of age, Board eligible, military duty completed. Passed National Boards, and wishes to practice with a group or an associate in a large community.

PLACEMENT OPPORTUNITIES

OBS-GYN—Board certified Obs-Gyn needed to associate with another Obs-Gyn in a large industrial city in Southern Connecticut, leading to eventual partnership. Hospital staff privileges available at two community hospitals.

HEALTH DIRECTOR—City of Stamford, population 100,000 needs physician with a degree in Public Health, with administrative experience, and willing to assume leadership in expanding and co-

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oxyphenbutazone

Tandearil in Painful Shoulder

Therapeutic Effects: Stiffness and pain may diminish within 2 days, and full mobility may be restored within a week. These effects are obtained with oxyphenbutazone alone or combined with physiotherapy or local hormonal injections. The drug is usually well tolerated and does not affect pituitary-adrenal function or immune response.

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage. Make regular blood counts. Discontinue the drug and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Painful Shoulder: 600 mg. daily in divided doses for 2 to 3 days; 300 mg. daily thereafter. Usual duration of therapy: 2 to 7 days.

Availability: Tablets of 100 mg. 6562-VI(B)R

For complete details, please refer to full prescribing information.

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ordinating the health activities of a community, can command salary equal to or higher than any in the area. Contact: Frank H. D'Andrea, M.D.; Chairman, Health Commission; 750 Summer St., Stamford, Connecticut 06902.

PHYSICIAN with a background in internal medicine and/or pediatrics who is interested in a group practice in a rural town in Southern Connecticut. Hospital services available at several area hospitals.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

STUDENT MEMBERS

Thomas W. Glynn, Burlington Rd., Unionville, Conn.
University of Kentucky Med. Ctr. - Class of 1967
Pre-Med: University of Connecticut
Parent: James Glynn

James R. Missett, 1790 Boulevard, West Hartford
Yale University - Class of 1970
Pre-Med: Catholic University and St. John's University
Parent: James S. Missett, M.D. (deceased)

Welcome New Members . . .

New Haven County Medical Association

Irvin M. Braverman, M.D.—789 Howard Avenue, New Haven, Connecticut 06504

Gordon S. Cohen, M.D.—310 Cedar Street, New Haven, Connecticut 06510

Wilbur W. Esdaile, M.D.—446 Dixwell Avenue, New Haven, Conn. 06511

Harris C. Faigel, M.D.—123 York Street, New Haven, Connecticut 06511

John Favata, M.D.—1389 West Main Street, Waterbury, Connecticut 06708

Sara B. Goffinet, M.D.—Milford Hospital, Milford, Connecticut 06460

Stanley W. Jackson, M.D.—333 Cedar Street, New Haven, Connecticut 06510

Harvey Jacobson, M.D.—646 George Street, New Haven, Connecticut 06511

Irving B. Joffe, M.D.—130 Division Street, Derby, Connecticut 06418

Michael Kashgarian, M.D.—310 Cedar Street, New Haven, Connecticut 06510

James D. Kenney, M.D.—309 Edwards Street, New Haven, Connecticut 06511

Samuel M. Lerner, M.D.—Yale-New Haven Hospital, New Haven, Connecticut 06504

Henry Mass, M.D.—98 Sherman Avenue, New Haven, Connecticut 06511

James W. Prichard, M.D.—333 Cedar Street, New Haven, Connecticut 06510

Joseph D. Saccio, M.D.—158 Whitney Avenue, New Haven, Connecticut 06511

Jules C. White, M.D.—309 Edwards Street, New Haven, Connecticut 06511

CONNECTICUT HEART ASSOCIATION ANNUAL MEETING TO FOCUS ON CONNECTICUT REGIONAL MEDICAL PROGRAM

May 24th

The Connecticut Heart Association Annual Meeting will be held Wednesday, May 24 at the Hillandale Country Club, Trumbull, Conn.

Henry T. Clark, Jr., M.D., Planning Director of the Connecticut Regional Medical Program, will be the keynote speaker. A Reactor Panel will query Dr. Clark on future plans of the C.R.M.P. as it relates to the Heart Association, community hospitals and community health facilities.

Invitations and programs are being sent to all health agencies and members of the Connecticut Heart Association. Further information is available from your local heart association or CHA, 65 Wethersfield Avenue, Hartford 06114.

Measles Vaccine Is Safe And Effective

Extensive clinical tests show that a type of measles vaccine now in use consistently gives a high degree of immunity with only one immunization and without causing rashes or illness.

The safety and effectiveness of the vaccine should make the task of eliminating measles in this country somewhat easier.

A report of tests on 14,000 children in the U.S. and Mexico appears in the current Journal of the American Medical Association.

The commercially available vaccine is termed a "highly (or further) attenuated live vaccine."

Two other types of measles vaccine are available and are effective. One type, however, has caused rash and temperature in 40 to 50 per cent of all children immunized, the report said. The second type does not cause significant reactions, but a series of injections is necessary to produce satisfactory measles protection. In some cases, this immunity has been relatively short-lived.

Clinical tests of the highly attenuated type of vaccine were done in Chicago, Cleveland, Detroit, Norfolk Va., and Mexico City.

"It was very unusual," the report said, "for a vaccinated child to show more than two or three of the symptoms usually seen with natural measles." In most cases, these symptoms were a mild rash or a slight temperature.

WOMAN'S AUXILIARY

President
Mrs. John D. O'Connell, West Hartford

President-Elect
Mrs. Anthony Cipriano, Hamden

First Vice-President
Mrs. Henry Sherwood, Middletown

Second Vice-President
Mrs. Edward P. Allen, Orange

WOMAN'S AUXILIARY CONNECTICUT STATE MEDICAL SOCIETY

Recording Secretary
Mrs. Nicholas Creaturo, Trumbull

Corresponding Secretary
Mrs. Irving H. Krall, West Hartford

Treasurer
Mrs. Forest D. Gibson, Farmington

Pree-Teen And Teen-Age Convention Program

Headquarters—Shelburne Hotel, Atlantic City — Shannon Hall

June 18 to 22

A special program, combining the area's seaside and boardwalk activities with fascinating historic sightseeing, has been planned for children of AMA and auxiliary members in Atlantic City during convention week, June 18 to 22. The program will be handled by Gulliver's Trails, Inc., under the auspices of the AMA Woman's Auxiliary. All water sports and beach activities will be carefully supervised. Teenagers and preteens will be in their own groups at all times. Monday and Tuesday must be taken as a combined package tour, and all activities include lunch, transportation and other expenses.

Please make advance reservations on the attached form. Registration will be on Sunday at 11:00 A.M. in Shannon Hall at the Shelburne Hotel.

Mrs. Philip J. Kunderman, Chairman
Mrs. Howell Cook, Co-Chairman
Teenage Program Committee

Monday, June 19—9:30 A.M.-4:30 P.M.

Boat Trip and Boardwalk Program. See Altantic City on a $1\frac{1}{2}$ hour sightseeing voyage circling the island; after lunch, a behind-the-scenes tour of a salt water taffy factory. A visit to Tussaud Wax Museum where the notables of history virtually come to life, and then a choice of either pool or ocean swimming, ice skating or behind-the-scenes tour of National Aviation Experimental Center (radar equipment, airport lighting system, etc.).

Tuesday, June 20—9:30 A.M.-4:30 P.M.

Island Excursion and Smithville. Escape to your own private Brigantine Island for sports, games, speed boat rides, water skiing and aquaplaning for those with parental permission (slight charge for use of equipment) and a picnic lunch. Special treat: rolling chair ride on boardwalk. Then a tour of the Towne of Smithville, historic restoration village, and its General Store with penny candy and knickknacks, Pot Pourri Shop and many other quaint shops. This village is a New Jersey landmark.

All-inclusive price with lunches for Monday and Tuesday: one child—\$23.00; two or more children in one family—\$21 each. Monday and Tuesday daytime tours must be taken as a combined tour.

Wednesday, June 21—9:30 A.M.-4:30 P.M.

Historic Philadelphia. A full-day tour of our "Cradle of Liberty." Major highlights include Independence Hall, Betsy Ross House, Christ Church (where Ben Franklin is buried), Franklin Institute with push-button exhibits covering aviation, science, astronomy. If time permits, tour will include a visit to the U.S.S. Olympia (Commodore Dewey's flagship).

All-inclusive price with lunch: one child—\$11.50; two or more children in one family—\$10.00 each.

Atlantic City, Batsto Area and Stage Coach Ride. Tour highlights of Atlantic City such as Absecon Lighthouse with its spiral staircase and observation tower; on to Batsto, restored Revolutionary War iron town. See a grist mill, old forge, Batsto Mansion. Then take a stage coach ride through the area. Pool swimming in late afternoon.

All-inclusive price with lunch: one child, \$11.50; two or more children in one family—\$10.00 each.

EVENING PROGRAM

Tuesday, June 20—7:00 P.M.-12:30 P.M.

Teen-agers. Dinner, Rides on Boardwalk and Bowling Tournament. A festive dinner, then on to the Million Dollar Pier for rides and wind up the night with a bowling tournament. A first-run movie offered for those who do not want to bowl.

All-inclusive price, including dinner, \$12.50.

OBITUARIES

Ronald H. Kettle, M.D.
1902 - 1967

Dr. Ronald H. Kettle, former superintendent of ie Norwich Hospital, died February 2, 1967 at Iartford Hospital, a few months after his retireient. Born in Burford, Ontario, Canada, he reeived his medical degree at Queens University, ingston, Ontario in 1928. Following an interniip at Hamilton General Hospital, Hamilton, Onirio, he became a resident at McLean Hospital, elmont, Massachusetts, where he remained until 931. He had additional post-graduate training at he Massachusetts General Hospital in Boston and t The Institute of Hospital Administrators.

Dr. Kettle's career at the then Norwich State Hospital began in 1936 when he joined the staff s a senior physician. His capabilities were rapidly recognized and he was appointed assistant superintendent in 1940. This post was relinquished in 1942 when he joined the U. S. Army Air Corps, receiving specialized training at the School of Aviation Medicine, Randolph Field, Texas, where he was qualified as a Flight Surgeon.

Dr. Kettle's military career was distinguished; he became chief psychiatrist of the 20th Air Force in Guam, with the rank of Lieutenant Colonel. After discharge from the service in 1946, he returned to the Norwich Hospital and was appointed superintendent the following year. In addition to his duties as superintendent, he lectured in psychology and psychiatry at the University of Connecticut and at Yale. In 1955 he was elected president of the New England Psychiatric Association. He was a member of the county and state medical societies, the American Medical Association, and a Life Fellow of the American Psychiatric Association.

Of the many contributions Dr. Kettle made to mental health in the State of Connecticut, he was particularly proud of his achievement in attaining full accreditation for a three year residency training program at Norwich Hospital. This accomplishment immeasurably increased staff competency and morale and, more importantly, the quality of patient care.

Dr. Kettle's administration was marked by firm convictions regarding treatment and administration, yet his mind remained open to advancement in psychiatric techniques so that the function of the hospital was never stagnant. He will long be remembered for his contribution to psychiatric administration and will be recalled as a warm friend, wise teacher, and physician-humanitarian in the finest tradition. It is most appropriate that the Intensive Care Unit of Norwich Hospital is named in his honor.

Claude Ballard, M.D.

Julius Harry Grower, M.D.
1898 - 1967

On March 1, 1967, Dr. Julius Harry Grower, age 69, died at the Middlesex Memorial Hospital following a long illness. He had practiced general medicine in Middletown, Connecticut for the past forty years and devoted himself unstintingly to the care of all who had sought his kindly counsel. To his many friends and devoted patients he will always be remembered as a gentle, kind and sincere physician dedicated to his profession and always available to those in need of his services.

For several years having been afflicted with the complications of circulatory disease, he had been semi-invalided, necessitating his retirement from active practice. During this interim, he was constantly attended by his devoted wife, Minnie. To those of us who were fortunate enough to know Julius intimately, it was always refreshing to find him cheerful and optimistic even during periods of great personal discomfort.

Dr. Grower was involved in many professional and civic activities. He was active in the establishment of The American Academy of General Practice and was an early past president of the Connecticut Chapter. He was a past president of the

Middlesex County Medical Association, member of Congregation Adath Israel, Middletown B'nai B'rith, St. John's Lodge No. 2, A.F. and A.M., Lady Washington Chapter O.E.S., Middletown Lodge B.P.O.E. He was a graduate of the University of Missouri and the University of Nebraska Medical School and did post-graduate work at Rotunda Hospital in Dublin, Ireland, Yale-New Haven Hospital in New Haven, New York Medical School and Cook County Graduate School, Chicago, Illinois.

He is survived by his wife, Minnie Shapiro Grower, two daughters, Mrs. Leonard (Bernice) Bonchi and Mrs. Daniel (Joanne) Bloom and two granddaughters.

To his family, we, of the Middlesex County Medical Society, extend our heartfelt sympathy at their great loss of a devoted husband and father. They may take comfort in the knowledge that his life will be an inspiration to others who remember his strong family devotion, his professional dedication and his courage and optimism during his long illness.

Philip E. Schwartz, m.d.

Alfred Bernard Vandersluis, M.D.
1930 - 1967

Dr. Alfred Vandersluis died at Lawrence and Memorial Hospitals, New London on February 27, 1967. His illness became apparent one month after he opened his own practice in obstetrics and gynecology.

Alfred B. Vandersluis was born in Cleveland, Ohio the son of immigrants from the Netherlands. He attended Baldwin Wallace College, Berea, Ohio where he received his B.S. degree and graduated in 1955 from the College of Physicians and Surgeons, Columbia University, New York. He served an internship at Strong Memorial Hospital, Rochester, New York. From 1957-1959 he was a Captain in the Army Medical Corps. He took his residency training in obstetrics and gynecology at Woman's Hospital, New York.

Dr. Vandersluis came to New London in Januar 1963 to enter an association and to join the staff o Lawrence and Memorial Hospitals. He became member of the New London County Medical Association and Connecticut State Medical Society. dedicated colleague with great enthusiasm and hop for achievements during his life, he was particularl interested in prevention and treatment of cancer He was president of New London Unit, America Cancer Society from 1964-1966. During these tw years an outstanding program took place in cance prevention, detection and therapy. It was at thi time when he himself became a cancer patient.

There followed months of despair, hope, pain faith and work. But hope and faith were strongest

"The woods are lovely dark and deep
But I have promises to keep
And miles to go before I sleep
And miles to go before I sleep

These words written by Robert Frost were cherished by him and shared with others during his illness.

He leaves his wife Ann, his daughter Wendy and his son Steven, his parents and two brothers. To them the Connecticut State Medical Society extends its deepest sympathies. He also leaves many friends who will remember his dedication and to whom he will always be an inspiration to carry on where he could just begin.

Frederick R. Behringer, m.d.

In Memoriam

Connors, Edwin R.—Bridgeport; Boston University School of Medicine, 1931. Dr. Connors had been a general practitioner in the Bridgeport area for 28 years, before being appointed medical director of the State Welfare Department. During World War II, he served in the Army Medical Corps with the rank of captain. Dr. Connors was the medical examiner for East Bridgeport for nine years. He had served as senior attending and chief of the general practice division at Bridgeport Hospital. He was a past president of the Bridgeport Medical Association and also served the association as secretary and vice president. He was president of the Connecticut Academy of General Practice. He was also a former member of the board of trustees of the Fairfield County Medical Association and served as secretary for six years. He was a member of the Bridgeport Medical Association, the Fairfield

ounty Medical Association, the Connecticut State
Medical Society, and the American Medical Asso-
iation. Dr. Connors died March 18 at the age of
4.

Deschamps, Stephen H. — Bridgeport; Columbia
College of Physicians and Surgeons, 1947. Dr. Des-
hamps was a specialist in internal medicine and
astroenterology in the Bridgeport area for many
ears. He was on the active staff of St. Vincent's
Hospital and on the courtesy staff at the Bridge-
ort Hospital. He was a member of the Fairfield
County Medical Association, the Connecticut State
Medical Society, the American Medical Associa-
on, the American Board of Internal Medicine,
nd the New York Academy of Medicine. Dr Des-
hamps died January 19, at the age of 42.

O'Keefe, David F.—West Hartford; Columbia
College of Physicians and Surgeons, 1929. Before
oming to Hartford, Dr. O'Keefe was chief director
f the Skin and Cancer Hospital in New York
City. He was a physician at United Aircraft Cor-
oration for 16 years. He was a member of the
Hartford County Medical Association, the Con-
ecticut State Medical Society, and the American
Medical Association.

Sutton, John E.—Washington; Cornell Univer-
ity School of Medicine, 1920. Dr. Sutton was an
x-member of Squadron A New York State Guard,
n which he served as colonel, commanding the
medical detachment during World War II. He was
member of the Association of Military Surgeons.
Dr. Sutton was on the staff at New Milford, Sharon,
nd Charlotte Hungerford Hospitals. Before com-
ng to Washington, Dr. Sutton was associate attend-
ng surgeon at the New York Hospital, a staff mem-
ber of the second service at Bellevue Hospital, and
n associate of the surgical staff at Flower Fifth
Avenue Hospital. He was a past president of the
Litchfield County Medical Association. He was a
member of the Litchfield County Medical Asso-
ciation, the Connecticut State Medical Society, and
he American Medical Association. He was a fellow
of the American College of Surgeons. Dr. Sutton
died March 20, at the age of 74.

Turkington, Charles H.—Litchfield; Johns Hop-
kins Medical School, 1907. During World War I,
Dr. Turkington was an instructor in tuberculosis
and thereafter became chief and consultant in
uberculosis at the Walter Reed Army Hospital.
He was a visiting physician at Charlotte Hunger-
ford Hospital and then became chief of medical
ervice. He was a member of the board of gov-
ernors and a fellow of the American College of
Physicians. He was past president of the Connecticut State Medical Society and the Litchfield County Medical Association. Dr. Turkington was a member of the Litchfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr Turkington died February 22, at the age of 86.

Special Notices

THE CHILDREN'S HOSPITAL OF PHILADELPHIA
and
The Department of Pediatrics, School of Medicine
University of Pennsylvania
Announce
A FIVE DAY REFRESHER COURSE IN PEDIATRICS
For Pediatricians and General Practitioners
May 1 — May 5, 1967

The Curriculum will consist of Lectures and Clinics, given by members of the Faculty Staff, in selected aspects of Contemporary Pediatrics in which important advances are being made.

AAGP accredited for 27 hours
TUITION IS $175.00
Registrations and Inquiries should be sent to:
CHILDREN'S HOSPITAL OF PHILADELPHIA
Post Graduate Education Committee
1740 Bainbridge Street, Philadelphia, Pa. 19146
Make Checks Payable to:
The Children's Hospital of Philadelphia

BOOKS RECEIVED

Congestive Heart Failure. Edited by Ralph M. Myerson, B.S., M.D., F.A.C.P. and Bernard H. Pastor (deceased), A.B., M.D., F.A.C.P. The C. V. Mosby Company, St. Louis, 1967, 174 pp. Illustrated. $12.85.

The Extremities. Third edition, edited by Daniel P. Quiring, Ph.D., and John H. Warfel, Ph.D. Lea & Febiger, Philadelphia, 1967. 124 pp. Illustrated with 110 engravings. $3.90.

The Head, Neck and Trunk. Third edition, edited by Daniel P. Quiring, Ph.D., and John H. Warfel, Ph.D. Lea & Febiger, Philadelphia, 1967. 128 pp. Illustrated with 111 engravings. $3.90.

Principles Of Biomolecular Organization. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol., and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1966, 141 illustrations, 491 pp. $15.00.

Ethics In Medical Progress: With special reference to transplantation. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1966, 257 pp. $11.75.

New Snakebite Treatment

A Miami surgeon has developed a new technique for treating snakebite: immediately cut away a half-dollar layer of tissue around the bite.

Getting rid of this venom-filled tissue as soon as possible is "the most effective treatment," according to Clifford C. Snyder, M.D. The technique marks a considerable departure from the traditional cross-cutting of the bite and drawing-out of the venom.

Dr. Snyder's successful treatment of 32 snakebite victims in the past two years is reported in the Medical News section of the Journal of the American Medical Association.

Immediate tissue removal could be done by a bitten person, Dr. Snyder noted. A relatively shallow cut the size of a large coin probably would get rid of most of the easily recognizable venom-killed tissue.

Not many persons would be able to perform this task, however, due to the shock of the bite and other factors, Dr. Snyder admits. A simple slash across the bite wound would be an alternate measure preceding the more radical treatment.

A tourniquet will prevent the venom's spread until a physician can perform the excision, Dr. Snyder said. The tourniquet should cut off only superficial circulation; it should be possible to insert a finger between the tightened bandage and the skin.

It's important that a tourniquet be applied immediately, Dr. Snyder said. Later, at the physician's office or hospital, additional tissue may be removed and antivenom administered through the artery serving the bitten area.

Despite the well-known tissue-killing effects of a snake venom, no amputations have been necessary in Dr. Snyder's 32 patients.

Five of those treated were bitten by cottonmouth moccasins and 27 by rattlesnakes. About 87 per cent of snakebites in the U.S. are inflicted by the rattlesnake.

Dr. Snyder is associate professor of surgery at the University of Miami and is a plastic surgeon in private practice. Associated with him in continuing research on the technique are Robert P. Knowles, D.V.M., instructor in animal surgery at the University's department of surgery; Maxwell M. Sayet, M.D., clinical associate professor of pathology; James Pickens, a senior medical student at Miami, and James Emerson, sophomore dental student at Ohio State University. William Haast, herpetologist and director of the Miami Serpentarium, also is assisting in the work.

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Around The State

New Haven County

183rd Annual Meeting
New Haven County Medical Association
March 30, 1967

The 183rd Annual Meeting of the New Haven County Medical Association was held at the Waverly Inn, Cheshire, Connecticut on Thursday, March 30th.

The session was opened by Dr. Max Caplan of Meriden, as presiding officer.

With the audience standing, the Clerk, Dr. H. A. Levin read the necrology. This was followed by a period of respectful silence.

When the meeting was called back to order, guests were introduced. We were again honored by the presence of the President of the Connecticut State Medical Society, Dr. Orvan Hess; the President-Elect, Dr. E. Tremaine Bradley; Vice-President, Norman Gardner, represented himself and Middlesex County.

The absence of delegates from the other counties, Fairfield and Middlesex excepted, was conspicuous on roll call.

The clerk reported our membership is now 1,019. Sixteen new members to be elected at this session will bring the roster up to 1,035. Incidentally, our indoctrination ceremony meeting has again been very worthwhile.

Officers elected at the annual meeting are:President, Bernard A. Burnham, Waterbury; Vice-President, Charles C. Verstandig, New Haven; Clerk, Hyman A. Levin, New Haven; Member Executive Committee, Max Caplan, Meriden.

Members to the House of Delegates and Alternates also made up the slate.

The meeting was productive of several resolutions which were thoroughly and openly discussed. In part, these dealt with Legislative matters, Title XIX and State Welfare Department, the County Hospital Plan, and the appointment of an Ad Hoc Committee to review structure, aims and purposes of a county society.

The meeting was followed by a social hour and dinner with wives as guests. At that time a report by Mrs. John J. Mendillo, President of the Woman's Auxiliary, and the presentation of the Past President's plaque to retiring President, Dr. Max Caplan, were preliminary to a most relaxing, mirthful and interesting hour of entertainment provided by Miss Pattie Bayne and Mr. Al Flosso, the latter billed as "The Coney Island Fakir."

Respectfully submitted,
H. A. Levin, m.d., *Clerk*

News From Yale University School Of Medicine

An expanded program of basic research on drugs that may prove useful in the treatment of cancer, mental illness, and other diseases will be undertaken in 12 newly completed laboratories for pharmacology at the Yale School of Medicine.

The laboratories, constructed at a cost of nearly half a million dollars, were dedicated at ceremonies recently. The new facilities were made possible by a grant of $230,000 from The Wellcome Trust of London, England, with matching funds from the U. S. Public Health Service.

Located in a renovated section of Sterling Hall of Medicine, the new laboratories will increase the area devoted to basic research facilities in the Department of Pharmacology by approximately forty per cent, according to Dr. Arnold D. Welch, Eugene Higgins Professor of Pharmacology and Chairman of the Department.

Two main fields of research in the Department of Pharmacology are cancer chemotherapy and neuropharmacology. Recent investigations in the former area by Yale scientists led to the development of the first drug, 6-azauridine, to have selective toxicity for at least one type of human cancer cell and almost none for normal human cells. It is now being used experimentally with great success in the control of psoriasis, a severe proliferative skin disease.

Another drug, 5-iododeoxyuridine, developed at Yale in the search for anti-cancer compounds, has proved highly effective in combatting several virus infections in man and is in widespread clinical use for the treatment of herpes infections of the eye. The drug is now being tested for its effectiveness against small-pox in clinical trials in India.

Participants in the dedication of the new pharmacology laboratories included, in addition to Lord Franks and Dr. Welch: Dr. Vernon Lippard, Dean of the Yale School of Medicine; Charles H. Taylor, Jr., Provost of Yale; and Dr. George H. Hitchings, Vice President in charge of research, Burroughs Wellcome and Company of Tuckahoe, New York.

Dr. Morton M. Kligerman, Professor and Chairman of the Department of Radiology, is the principal investigator in the program. The co-principal investigator is Dr. Paul Howard-Flanders, Professor of Radiobiology and Molecular Biophysics.

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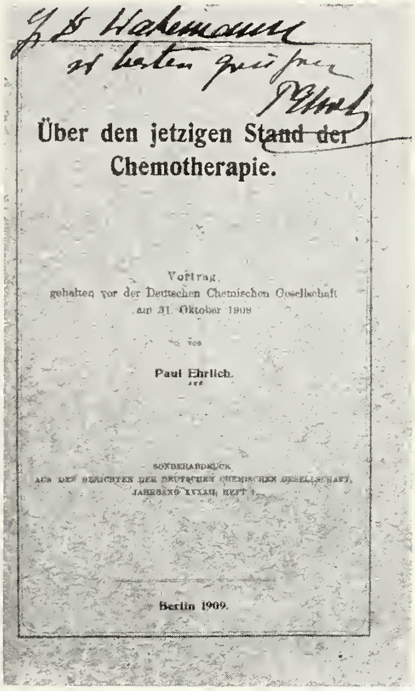

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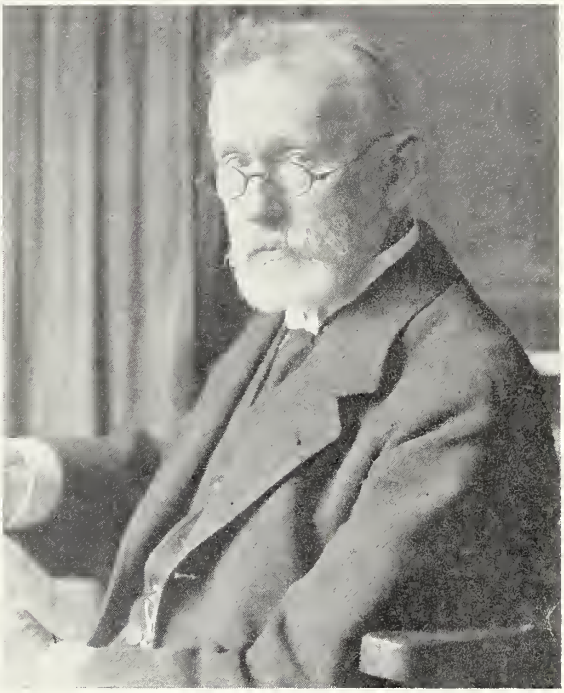

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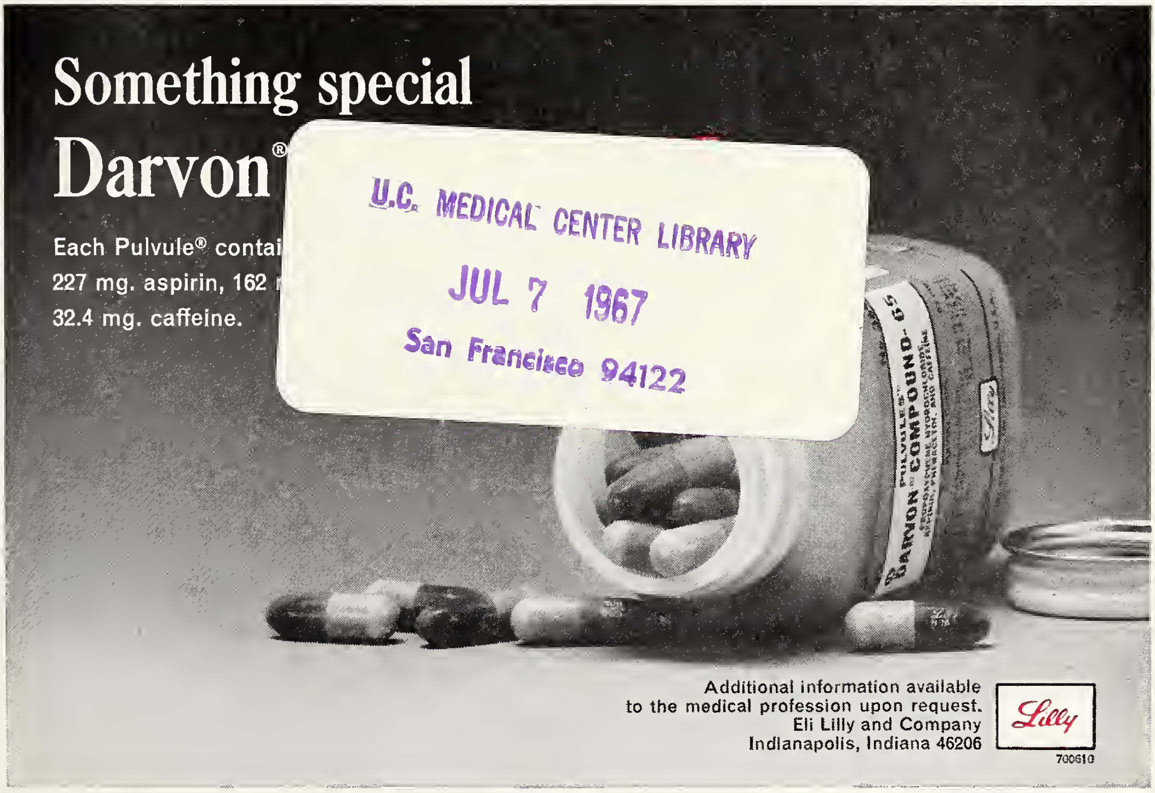

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Connecticut Medicine

editorials

Factors In the Formation Of The Red Thrombus

It is now recognized that pulmonary embolization occurs much more frequently than its clinical recognition would lead us to believe. In fact some instances of relatively massive pulmonary embolization occur without it being suspected by the physician.[1] Since pulmonary emboli arise on the venous side and have the characteristics of a red thrombus (except in the rare instances of fat emboli) it is pertinent to consider its pathological structure as well as the factors that lead to its formation.

The red thrombus formed *in vivo* resembles the blood clot formed *in vitro*. It consists of a meshwork of red cells and fibrin in which platelets are trapped in random fashion. Also significant is the fact that the red thrombus forms most frequently in areas of retarded blood flow, in which the wall of the blood vessel may be entirely normal. One idea about the primary factor that leads to formation of a red thrombus is the activation of the intrinsic coagulation mechanism, a sort of transient local hypercoagulability.[2] What seems not clear at this time is the nature of the stimuli that spontaneously activate the intrinsic coagulation mechanism. Do they arise in the general circulation, or only locally in areas that are predisposed to thrombosis? One thing is known namely that stasis is necessary for the red thrombus to form.

Stasis provides two functions: it prevents dilution of activated blood coagulation factors by blood flow and it also prevents the clearance of activated blood coagulation factors by hepatic mechanisms. Not surprisingly therefore, the red thrombus is found almost exclusively in the venous circulation. When it is formed in the arterial circulation, it is present as a propagating red tail that forms distally behind an occlusive lesion. It then grows and extends up a static column of blood until it reaches a point of entrance of a collateral vessel.

Stasis alone seems not to be sufficient to cause a red thrombus to form. In laboratory animals a red thrombus will not form unless the intrinsic blood clotting system is activated as well, much as occurs in disseminated venous thrombosis. The view that stasis alone will not lead to red thrombus formation is supported by the speed with which a red thrombus can form. A massive red thrombus can form within ten minutes if the stimulus for activation of the intrinsic coagulation system is sufficiently intense.[2] We also know when we sit with legs dependent or crossed that profound stasis does occur and this stasis may remain for hours without thrombi forming. However in such a position in the presence of a sufficient stimulus there is plenty of time for a red thrombus to form.

It is this knowledge of the factors involved in red thrombus formation that explains the efficacy of anticoagulation therapy. A red thrombus arises primarily from alterations within the blood clotting system itself. One might therefore expect that anticoagulants by retarding intravascular clotting would be effective in the prevention of red thrombus formation. This certainly has been shown to be true in carefully controlled clinical studies.

L.H.N.

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THE COVER

ALTHOUGH he had already won the Nobel Prize in Medicine for his work in immunity, Paul Ehrlich (1854-1915) is most known for his discovery of the "magic bullet"—Salvarsan (606). Perhaps more significant than the compound itself was the demonstration of the value of the application of rational biochemical principles in the search for antimicrobials. Though he coined the term chemotherapy in reference to the treatment of infectious processes with drugs, this term and similar principles have now been applied to the search for effective antineoplastic agents.

The Accident And The Injury

Injuries from motor vehicle accidents are the primary cause of death between five and twenty-four years of age and it is a rare week that does not bring to the medical examiners office in any large city several young people whose lives have been ended as a result of such accidents. Luongo[1] has pointed out that since the advent of the automobile until 1966 more than 1,500,000 people have lost their lives from injuries resulting from motor vehicle accidents and hundreds of millions have been injured and billions of dollars worth of property have been lost.

Ralph Nader's crusade against the giant automobile industry resulted in federal legislation and a general public awareness that much more could be done to provide safer vehicles. However the road to safer cars will not be an easy one, since the demands of the powerful automobile industry has forced significant compromises in the standards originally proposed by the National Traffic Safety Agency headed by Doctor William Haddon. A major reason for the compromises Luongo points out was the need to lessen the stumbling block that the proposal placed in the way of international trade and tariff negotiations.[1] In other words national and international forces interested only in profit are standing in the way of legislation that places a premium on automobile safety and human welfare.

There has been in recent years an awakening interest on the part of the medical and legal profession in the study and prevention of traumatic injury. Now as prevention and care of infectious and degenerative diseases is becoming more possible, trauma looms larger as an area of medical concern. It is time for us to look at automobile fatalities and injuries as a pathologic entity to determine their etiology and sequelae in order to undertake appropriate preventive measures.

Until recently research into automobile accidents has been carried out largely in a haphazard manner. The car, the driver, the highway in turn were scrutinized for the key to the automobile-accident syndrome. The time is now for us to study automobile accidents in a total sense and to do so with an approach that involves many discipline. Alan Nahum at U.C.L.A. has been studying the causes of injury to motorists in automobile collisions with the aid of physicians, engineers and photographers. They conduct a detailed examination of all persons injured in selected traffic accidents. They have arrived at a description of the accident and how the injuries occurred.

The majority of injuries they found are sustained while passengers are inside the car. Being ejected from the vehicle is almost always more dangerous than remaining inside. If the motorist cabin remains intact, most of the injuries sustained inside the vehicle could be prevented. But remaining inside, the passenger injuries are due to collision with some area inside the vehicle. The causative agents inside the vehicle in the order of importance were the steering wheel and column, the instrument panel, the windshield, the doors and the A post, a support between the windshield and door, and finally the roof over the windshield.

There has been much discussion about the virtues and dangers of small cars. Nahum and his group found small cars inherently unsafe, because of decreased structural strength, less room for motion of passengers before striking the interior during a collision and the unequal collision with a large car in which the small car is apt to fare poorly and fail to protect its occupants.

The research underway at U.C.L.A. has revealed that man can withstand large collision forces if he is wearing proper restraining devices but that few people avail themselves of them even if they are available in the car. The problem then is to convince the motoring public of the value of these restraints. They have urged also modification of vehicle design by strengthening the protective shell of the motorist compartment and modifying such lethal areas as steering wheel and column and other surfaces which are within striking range of the "involuntary acrobatics forced upon motorists by collision forces."

The Boston University Law-Medicine Institute has also initiated a pilot study of single car fatalities in the meropolitan Boston area also with an interdisciplinary team. All facets of the accident are being studied in an effort to ascertain the cause of the "first collision" that is for example whether there was a persisting medical or psychiatric condition that could have caused the accident. Also whether there was a mechanical defect that was a causal factor, or whether there was a defect in highway maintenance or highway safety. Finally whether alcohol or drugs contributed to the accident.

Once these questions were thoroughly investigated, then the injuries sustained by the car occupants are carefully studied. What was the actual cause of death, which portion of the vehicle did the deceased strike? Was he ejected from the vehicle and what would have been the effect of restraining devices? Could a design change such as a collapsible steering wheel have prevented the death; do the collapsible steering wheels really collapse? Finally they are investigating what kind of emergency aid the victim received and whether a more efficient emergency system could have saved his life.

It is clear enough that the change in car design will be slow in coming and that the avoidance of accidents will also be a long drawn out task, whereas the immediate question of how to reduce the severity of injuries sustained already has answers. Nahum's studies clearly show that more than half of the present number of deaths and injuries could be prevented by proper restraining devices during a collision and appropriate modifications of vehicle design. It may be impossible to obtain any significant decrease in traffic accidents in the near future. Let us work on reductions of injuries to passengers by the means already known and available. The changes in car design necessary to reduce injuries are already known. Those who have resisted introducing them into car structure because they put the profit motive ahead of human welfare must bear a heavy responsibility for the continuing death and injuries resulting from automobile accidents. But the passengers who do not use adequate restraining devices are also contributing heavily to the mounting injuries and death toll on the highways.

L.H.N.

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More On Interferon

Professor André Lwoff, a Nobel Laureate, has reviewed all the findings with regard to what stops a virus infection and concluded that there are three factors other than antibodies that are implicated: elevated temperature, low tissue pH. and interferon production. Isaacs and Linderman,[1] in 1956, first demonstrated a soluble material they termed interferon which stops a viral infection. As a result of this classic study a great deal of investigation has been carried out which led to isolation, production and characterization of this important material.[2]

It has been known for over thirty years that infection with one virus interferes with the growth of a second one. For example as far back as 1803, Erasmus Darwin noted that vaccinating a child against smallpox will not take if the child is suffering from measles. In fact the vaccination can only take after nine to eleven days when, as we know now, circulating interferon no longer occurs.

Interferon seems to be active against a wide variety of viruses of both RNA and DNA types. In addition to the action of interferon locally in the control of growth of virus in an infected tissue of the body, it seems likely that circulating interferon can act at a distant site to protect against the spread of virus infection. Recent studies have shown that interferon if given prophylactically is active against certain of the oncogenic viruses including those that cause leukemia in mice and tumors in hamsters. Once the oncogenic virus has subverted the machinery of the cell then interferon is ineffective against the tumor.

Merigan[2] has been able to purify interferon and found it to be a neutrally charged protein with a molecular weight of 20,000 to 30,000. As a result of this achievement several experiments on viruses became possible. Interferon is now known to be produced in a wide variety of animals from fish to man. It appears to be produced in virus target organs but also in the reticuloendothelial cells and in the spleen and leucocyte.

Merigan and his co-workers have learned that not only viruses can produce interferon but also non-viral agents such as extracts of living material and higher organisms. The largest agent yet known to induce interferon is the intracellular protozoan toxoplasma. In the search for inducers of endogenous interferon, many macromolecular fungal products like statolon and helenine has been found effective and Regelson[3] found a synthetic polysaccharide of 17,000 molecular weight to be capable of inducing circulating anti-viral activity in the mouse. Work along such lines may open the path to control of viral infections as we now control bacterial infections by antibiotics.

Interferon has a high potency of anti-viral action. Apparently the same virus can produce different interferons depending upon which type of animal cell it infects. But multiple viruses can produce the same type of interferon if they infect the same animal species. Not only is it effective against virus but also against a member of a group of intracellular parasites such as psittacosis, lymphogranuloma venereum and also against trachoma agents.

It is interesting that interferon has no measurable effect on the host cell in any of its biosynthetic functions such as synthesis of DNA, RNA and protein. Interferon containing cells divide at a normal rate and antibody synthesis is not impaired after treatment with interferon. It appears there is no significant net absorption of interferon onto or into cells. It is exclusively an intracellular product.

An interferon protected cell does not prevent absorption and penetration of a virus into it. The uncoating activity—stripping the protein overcoat from viruses takes place, but there is a lack of formation of the viral specific polysome and this prevents the synthesis of viral-coded protein. No infectious viral particles—virions are formed or released. In aborting the virus multiplication and preventing its spread to the healthy uninfected neighboring cells, the invaded cell is sacrificed and dies.

In humans, interferon can be produced *in vitro* and is found *in vivo* in serum and other body secretions after natural as well as live viral-vaccine infections. Persons infected with mumps show interferon in the blood for three to four days after the onset of symptoms and its appearance seems to parallel the associated fever which represents the time of greatest viral tissue invasion and replication. However it has a short-half-life in the blood stream. In animal studies Merigan found much greater quantities are being poured into the circulation than is reflected in the serum level.

At present human interferon is being studied for two practical applications. One is to attenuate viral strains without reducing their immunologic action in the preparation of live virus vaccines. It has been done by serial passages with rubella and has been suggested for polio, mumps and hoof-mouth disease. A second practical application of our knowledge about interferon is in the control of clinical viral infection in man.

Locally applied monkey interferon is active against viruses in human cornea and the skin, but not against virus infections of the upper respiratory tract. In systemic rather than local virus infections the movement is toward administration of exogenously prepared human interferon and stimulation of endogenous interferon production. Exogenous interferon in man, Merigan points out, will require large quantities and the protection will be of relatively short duration because of the short half-life of interferon. Purified interferon seems still to be a long way off.

It is possible that there exist in some patients defects in interferon production. This may underlie the occasionally severe cases of vaccinia grangrenosa or other viral infections in patients with tumors or those on corticosteroid therapy.

There are already some anti-viral agents. One such is betathiosemi-carbazone and the question may well be asked whether this chemical acts like interferon or in some other way. Merigan believes the mechanism of action is different because it prevents virus replication without destroying the polyribosomes and therefore without sacrifice of the invaded cell.

L.H.N.

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A Peptide Inhibitor Of Calcification

A study of the solubility of calcium and orthophosphate reveals that normal serum is supersaturated with these ions. So are the extra cellular fluids with respect to hydroxyapatite. This is the form in which crystalline salts of calcium are invariably deposited in mammalian tissues. Normally this occurs in a controlled fashion at tissue sites such as bones, teeth and cartilage. Only under pathological circumstances are the same salts deposited in degenerated tissues and in extracorporeal areas such as the urinary and biliary tracts. However since the normal serum is super-saturated with calcium and phosphorus ions the question is why are there so few instances of pathological calcification? Indeed why do not all tissues calcify and turn into "pillars of stone." There must be a substance which prevents the catastrophes which would otherwise result from calcium deposition in the normal state.

Howard *et al*[1] were led to raise this question because the urine almost invariably contains a far higher product of calcium x phosphorus than is required by Kramer's[2] rule for hydroxyapatite deposition, and yet only a very small majority of individuals actually develop calcific urinary calculi. They found in fact no difference in Kramer's rule between normal and stone forming persons. The thought presents itself that perhaps there is present in body fluids and urine a substance that prevents calcium deposition, in other words an inhibitor of calcification. If so it would offer a clue towards an explanation of some previously enigmatic questions relating to biologic calcification. It might also shed light on the mechanism whereby large quantities of calcium and phosphorus can traverse cells without serious impairment of their function.

As a test object to determining the calcifying potential of a solution, they used ricketic cartilage. In normal urines the ricketic cartilage failed to calcify whereas the urine of stone formers induced calcification. By a variety of experiments they eliminated the possibility that it was magnesium concentrations that were involved and accordingly were led to seek for another substance. By a series of beautiful biochemical procedures they arrived at the isolation of an inhibitory factor, a urinary peptide which was also isolated from the plasma as well.

Once isolated and purified they found its action so potent that as little as three micrograms of the purified inhibitor prevented the reaction of calcium and phosphate to form hydroxyapatite, and also prevented the appearance of crystals. Apparently the peptide inhibitor is more potent against crystal formation without cartilage than with it. This could explain why we don't turn to stone and why we rarely form calcium stones in the urine.

We are fortunate that the inhibitor is more active in solutions than in cartilage, but why it is less active in cartilage is not clear. Perhaps there are already present hydroxyapatite crystals in the cartilage and they might presumably stimulate some crystallization from the solution. Perhaps some of the added inhibitor becomes bound to unreactive sites of the cartilage or bone.

The presence of a component in plasma which also possesses the ability to prevent the formation of hydroxyapatite crystals from super-saturated solution of calcium and phosphorus ions provides for the first time an experimental approach that should lead to clarification of the elements in the control mechanisms of endochondral calcification. It should lead us to a clearer understanding of the factors involved in spontaneous calcium phosphate deposits in degenerated tissues, the urinary tract and gall bladder.

Most of the inhibitory potency of whole urine can be accounted for by two similar peptides with a molecular weight of 580 to 950. The purified inhibitors contain aspartic acid, glutamic acid and a substituted aminoterminal residue. There should be very little difficulty in synthesizing a peptide of such low molecular weight once the structure of the peptide here described is identified. We also require to learn the tissue source of the peptides and finally its physiologic role. We may look forward to speedy answers to these questions.

L.H.N.

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Clinical Factors Influencing Drug Susceptibility

The desire to take medicine is one feature which distinguishes man from his fellow creatures.—Sir William Osler.

Two hundred years ago when there were hardly any drugs Sydenham complained "we are overwhelmed as it is with an infinite abundance of medicaments and here they add a new one." What would he say today when drugs are available in the hundreds and patients are receiving many drugs at one time, one of Smith's[1] patients having received as many as 37 different drugs at one time. The real astonishment is that under these circumstances there are so few reactions to the new potent pharmaceuticals rather than so many, although an incidence of almost 11 per cent bears close scrutiny.

Adverse pharmacologic effects or allergic reactions produced by drugs are obviously determined by two variables—Drug and Human. Some of the personal or clinical variables and factors influencing drug effects are known, but what we would like to be able to do is to predict which patients are most likely to have adverse reactions after administration of a drug or combination of drugs, in short the epidemiological personal variable or clinical factors which may be responsible for predisposition to the untoward effects of drugs.

Sydenham to the contrary, in the early days the physician had little in the way of effective drugs. His ability to treat disease was essentially limited to quinine, mercury for syphilis, digitalis and morphine. The other non-specific drugs he used generally were not hazardous. Now as then there is no drug that is absolutely safe and in general the more potent and complex a drug becomes the greater become the hazards in its use. Obviously we must balance off against these greater hazards, the greater advantages of a drug in saving life, in shortening illness and disability and promoting good health. Clearly, it is our responsibility as physicians to use drugs with discretion, to abstain from using potent and hazardous drugs for trivial conditions. But we must also know how to avoid some of the pitfalls involved in using drugs in the clinical situation.

Smith, Seidl and Cluff surveyed 900 hospitalized medical patients over a one year period for adverse drug reactions. As might be expected reactions were most common in patients with serious illness who received many drugs at one time. The overall adverse reactions found were about 11 per cent, but as the number of drugs reached 11 to 12 the adverse reactions grew in number also. One patient who had five different reactions received 37 different drugs! To be sure the most severely ill patients required and received the most drugs and accordingly had drug reactions more frequently.

Diuretics were not incriminated in reactions in patients receiving less than 11 drugs and intihypertensives and opiates were incriminated in reactions only in patients receiving more than 11 drugs. It didn't seem to be due to any particular combination of drugs and this should be further investigated.

Four patients developed gastrointestinal reactions to magnesium and aluminum hydroxide but they received more than 16 drugs! On the other hand reactions to digoxin remained unchanged whether the patients received 1 or 16 drugs.

The overall rate of adverse drug reactions were significantly increased in patients with abnormal

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renal function. This, however, applied only to certain groups of drugs such as tranquillizers and diuretics but not to digoxin or phenobarbital. It is possible that such patients have diminished renal blood flow and cannot excrete readily from the distal tubules drugs conjugated in the liver.

It is interesting that as liver function decreased only certain drugs such as sedatives and tranquilizers showed five times more drug reaction than did patients with normal liver fnuction. This probably is because such patients are unable to detoxify drugs adequately by conjugation with glucuronic acid in the liver due to impairment of the enzyme glucuronly-transferase.

As might be expected there was a slight increase of allergic reactions in atopic patients. But there was a large increase of allergic reactions in patients with gastrointestinal ailments and most were due to barbiturates, meprobamate and amitryptiline. Reactions were also more common up to 9.5 per cent in patients suffering from infections as compared to 1-5 per cent of patients without infections. Numerous agents were incriminated, 10 reactions to antibiotics, three out of four reactions to morphine and codeine in the form of apnoea, urticaria, maculopapular rashes. Allergic reactions were also more common in patients suffering from infections not due to the antimicrobial agents alone nor to abnormal renal function. Probably this occurred because of the large number of drugs —14—that these patients received.

When considering the specific drugs incriminated we find the whole spectrum of drugs employed although such drugs as barbiturates, meprobamate, codeine, penicillin, and thiazide diuretics were found most frequently associated with allergic reactions. Two deaths, one from agranulocytosis and sepsis was attributed to cyclophosphamide and another due to central nervous system depression was attributed to a combination of librium and phenobarbital. It also appeared as though nervous system depressants were more toxic at high temperatures.

Smith's study gives us some indication on the relation between drugs and diseases as to the likelihood of drug reactions. It points up the need for physicians to realize the likelihood of a drug producing a reaction in various disease states, in various combinations of drugs and most importantly to the relation to the number of drugs being employed at any one time.

L.H.N.

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Naturally Occurring Toxicants In Foods

We should be more aware and pay more attention to the variety of substances present in foodstuffs. There are now large numbers of extraneous substances in foods such as pesticide residues, as well as food additives. But we must not overlook those substances that are naturally present in foods. We must bear in mind that there are three ranges of intake for every substance. One is associated with physiological inertness, a second with physiological function or benefit, but also a third with potential hazard, for it has been recognized since the dawn of history that there are naturally occurring toxic substances in various plant and animal products.

A few plants which contain particularly toxic compounds have pharmacological properties useful in treating disease. This is how early therapeutic medicine was established on an empirical basis. Modern medicine and pharmacology still devote considerable attention to those plants that contain physiologically active substances such as digitalis purpurea and Rauwolfia serpentina. Thus roots of this latter substance were used as a hypotensive agent in India for many years before it received widespread recognition in other parts of the world.

The literature in this country relating to posionous plants increased tremendously between 1884-1900.[2] This was a period of rapid western expansion of agriculture which brought man and his livestock in contact with many new plants. The reports of toxicity during this period dealt mostly with farm animals and dealt with "loco" poisoning, crotalism, the toxicity of sorghums, lupines, castor bean and bittersweet.

Mikelson and Young point out the difficulty of presenting such a subject as naturally occurring toxins in food. Ideally one would like to group the toxic substances according to their mode of action. It is probable that most of the toxic substances act as antimetabolites even though we do not as yet know exactly with which metabolites they interfere. This is not true for all since some are normal constituents and are poisonous only when ingested in excessive amounts. For example, ordinarily liver is a highly recommended food from a nutritional point of view. But liver from polar bears is injurious. The toxicity of this food was known to Eskimos but not to early arctic explorers. Such men developed symptoms which were later shown to be associated with the ingestion of toxic levels of vitamin A.

This phenomenon is true in farm animals who frequently consume a large amount of a particular plant or one of its parts for long periods of time. If a toxic substance were present in the feed, then symptoms of poisoning might develop. This may

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occur even though the toxic substance were present in concentrations such that a lower or intermittent intake of the plant would produce no effect. Mikelson and Young consider only a few of the foods whose consumption is associated with certain toxic symptoms, especially in animals.

Soybeans when properly heated provide a protein of high biological value and are used extensively for both human food and animal feed. It was Osborne and Mendel who recognized that the growth promoting property of soybeans was greatly improved by cooking. The maximum improvement in the protein efficiency ratio occurred when the raw soybean meal was steamed at atmospheric pressure for 30 minutes. The inhibition to growth in the raw soybean ration is due to the presence of a trypsin inhibitor in raw soybeans which is destroyed by cooking. It appears that raw soybeans are not unique in containing a antitryptic substance since a water extract of many other beans also contains it, although wheat and corn are devoid of it. It is not yet clear how raw soybeans exert their growth depressing effects.

Cottonseed meal also has a toxic factor due to its content of a yellow pigment gossypol. The symptoms of toxicity are decreased growth rate, gastroenteritis and hemorrhages. Chicks develop anemia and stop laying eggs, or if small amounts of gossypol are present the yolks are discolored. Animals most sensitive to gossypol are guinea pigs, rabbits, swine, dogs. Least sensitive are rats and poultry.

Bracken fern also produces skin hemorrhages as well as in the internal organs, incoordination and opisthotonus. There has been numerous outbreaks reported in cattle and horses and appears to be due to a thiaminase which destroys this important vitamin in the gastro-intestinal tract. It is interesting that different animals tolerate different amounts of bracken fern.

Linseed meal was found to have a growth inhibiting substance in unheated linseed meal coming mostly from the cotyledons, but none in the mills isolated from the flaxseed. It has been found to be due to the presence of a pyridoxine antagonist.

Cycad is an especially important food which when eaten raw causes paralytic symptoms in sheep and cattle. Natives in Guam who have eaten cycad suffer from amyotrophic lateral sclerosis with a progressive incurable paralysis of the extremities. The Guamians use the nuts of the cycad both as an emergency source of food and to a lesser extent a regular part of their diet. Cycad is a palm-like tree that grows in many tropical and subtropical areas. The stems are 5-6 inches in diameter. The natives long ago realized that the kernels are toxic and attempted to eliminate the toxic substance which turned out to be a glycoside, by soaking the quartered kernels in water for 7-10 days. After the soaking process, most of the toxic substance is eliminated and the kernels are spread out to dry in the sun and ground into a fine powder that looks and acts like wheat flour. If the washing is inadequately performed the toxic substance may not all be washed out and this explains why amyotrophic lateral sclerosis is more than 100 times greater among the natives on Guam than among the inhabitants of this country or Europe.

Within the last few years evidence has been presented for the existence of a substance in certain types of raw fish which interferes with the absorption of iron. Young mink when fed a ration containing large amounts of raw coalfish become anemic and develop a light-colored underfur and 20-30 per cent died. If the fish were boiled prior to its incorporation in the ration, the difficulty was easily overcome. Even if fed raw fish, the anemia would not develop if iron were given parenterally. This of course means that the ingested raw fish interfered with iron absorption. The substance is also present in whiting and in much higher concentrations in hoke.

It is time to take stock of what knowledge we have about the effect of the dietary intake not only of the nutrients but of all the other multitudinous components of foodstuffs, on the way animals and man respond to them. Almost every biological investigation requires an understanding of the dietary factors that animals and man are ingesting. Elucidation of these factors may well constitute another major contribution of nutrition to the solution of the health problems of the 20th Century. Some of them will be dealt with in forthcoming issues of this Journal.

L.H.N.

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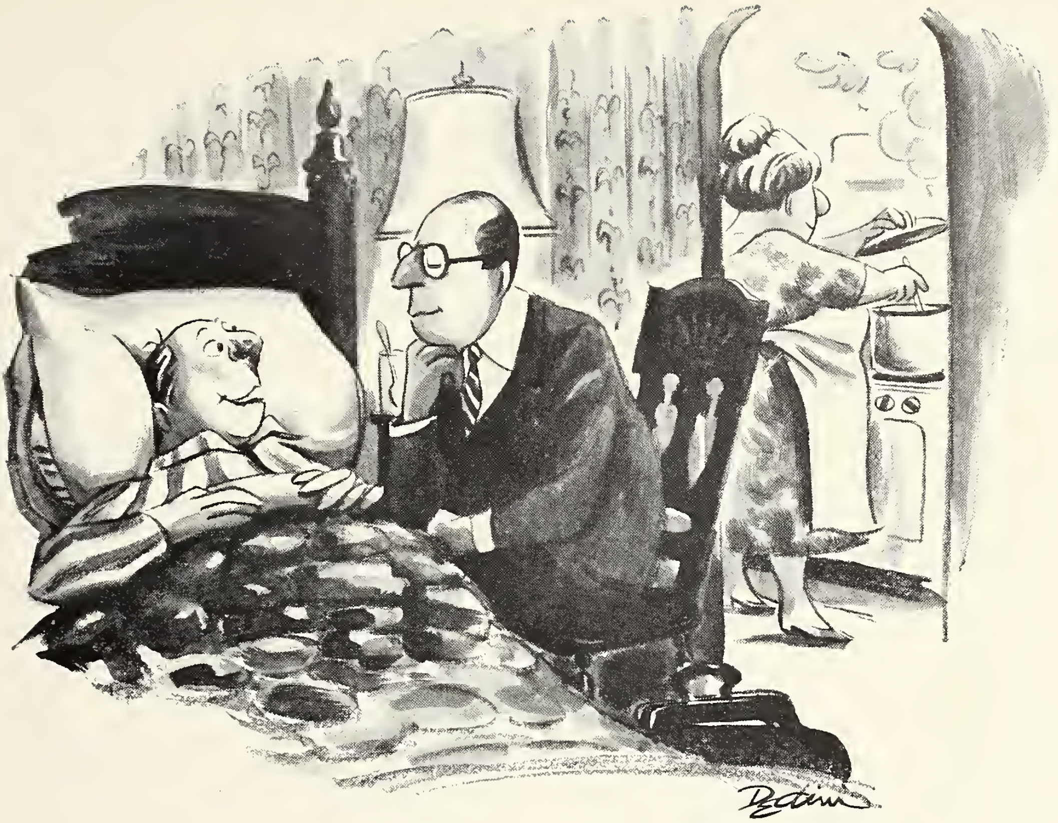
Recognizing Prediseases

Obviously all diseases which become chronic are asymptomatic in their early stages. Because they are asymptomatic patients do not seek a physician's help as they do for an acute illness in which they come to their physician because of not feeling well. In the acute illnesses, the task of the physician is to make the patient feel better or well. Asymptomatic patients in the early stage of a chronic dis-



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ease do not seek a physician's help. They are in a stage of what Mendlowitz calls a predisease.[1]

Arterial disease, hypertension, diabetes, gout and others characteristically become symptomatic in the fourth and fifth decades of life. However, they are recognized earlier because a biochemical test or a biophysical apparatus for their detection happens to be available at the present stage of our knowledge. It is known that these asymptomatic abnormalities sooner or later eventuate in symptomatic diseases as renal failure, blindness, coma. Nephrosis with edema, and acute arthritis even apart from their effects upon arterial disease itself, catastrophe such as strokes, heart attacks and peripheral gangrene do not complete the list.

It is characteristic of arterial disease to be asymptomatic in the early stages. It is not until the disease progresses to the point of producing ischemia of tissues supplied with blood that symptoms appear. Sometimes the symptoms may not become apparent until rupture of a weakened arterial wall with hemorrhage and destruction of surrounding tissue has occurred.[2] In addition there are the major "enemies" of the arteries, those diseases which constantly bombard them which themselves are asymptomatic in the early stages.

There are a whole group of abnormalities with which arterial disease is interrelated. There is a spectrum of lipid abnormalities, including hypercholesterolemia increased free fatty acids.[3] There are certain personality characteristics related to coronary artery disease. Patients with abnormal steroid responses, abnormal blood clotting factors[4] and with such acquired habits as smoking among others are "coronary prone." Very little is known about the real relationship of these prediseases to arterial disease itself. Several authors have speculated on mechanisms in cases of arterial disease which precede overt manifestations of diabetes.

When asymptomatic hypertension or diabetes is discovered it is treated in order to normalize abnormal blood pressure rather than to "cure." In this way it is believed that at least to some extent the arteries will be spared and the pace of their destruction diminished. When hyperuricemia is discovered it is treated so that renal damage from precipitation of urates in the tubules will be prevented. When diabetes is discovered it is treated to regulate or to normalize the blood sugar so as to prevent possible arterial injury later on. Thus there are a whole group of abnormalities which are not symptom producing but which may and probably will eventuate in symptomatic disease.

Then of course there is the other side of the coin therapy itself may produce side effects which may become more unpleasant than the disease itself. For example hypertension may require treatment for many years and some of the drugs used like the thiazides may produce electrolyte alterations, hyperglycemia, hyperuricema and even hypothyroidism in many patients. In consequence patients need to be convinced that they require treatment on the basis of knowledge and reason and not for the relief of symptoms they do not yet have. The treatment itself may produce new diseases such as hemolytic anemia, lupus erythematosus—like syndrome and other immunologic states. The effects of these may at any time be worse than the underlying disease left untreated.

Here then is a dilemma. All of this requires reorientation of teaching, reorientation of medical thinking about medicine as it is and about medicine as it is undoubtedly going to develop. But we need to keep in mind some of the new concepts on reaction to drugs used such as immuno-chemical mechanisms of drug allergy activation of lupus erythematosus by drugs, immunological basis of purpura due to drug sensitivity.

Since all diseases are in part genetically determined, it is clear that abnormalities that lead to the diseases must be present at birth and the terms prediabetes, prehypertension and pregout will begin to appear and methods for detecting such abnormalities which are now in various stages of development will be aggressively pursued. Hyperuricemia is easily detected, so is hypercholesterolemia. There are new testing procedures for prediabetes such as cortisone glucose tolerance test. In prehypertension, vascular reactivity tests and tritiated norepinephrine disappearance tests are on the horizon.

Effective therapy meanwhile is largely in the realm of preventive medicine. There is no rational therapy of predisease except in the sense that if we can detect them early we may be able more effectively to prevent a predisease from becoming a disease.

L.H.N.

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Patterns Of Epidemiologic Spread Of Viral Hepatitis

In 1961, the last peak epidemic year, 73,000 cases of viral hepatitis were reported in this country. If the cyclical pattern repeats itself as epidemiologists anticipate it will, we can expect many more thousands of cases by '68 or '69. Among our military troops viral hepatitis is still the leading single infectious disease causing the greatest loss of man hours daily. Inasmuch as no experimental host or tissue culture system has been found to be suitable for growth and propagation of these viruses, essentially all we know about these agents comes from a clinical and epidemiologic viewpoint in studies of spontaneously occurring human cases and from a very few experimental studies with human volunteers.[1]

We know from Paul Havens studies in 1945 that bacterial free filtrates derived from patients with the acute phase of the disease are able to induce viral hepatitis in susceptible human subjects. These viruses are serially transmissible in human subjects. However the viruses have not been isolated. They are the most stable of all known viruses, resist heat treatment at 56° C for over thirty minutes and some strains for as much as an hour. They withstand chlorination at one part per million for thirty minutes. Other chemicals that ordinarily inactivate bacteria and most other viruses are totally ineffective against hepatitis agents.

We now recognize multiple epidemiologic pattern of spread of viral hepatitis. One is person to person contact which is thought to be the most common type of transmission. In Koff *et al's*[2] study of viral hepatitis in a group of Boston City Hospitals, forty of one hundred and eighty five patients had definite contacts with jaundiced persons. Then there were sporadic contacts with acutely ill but non-jaundiced children.

Then there have been extensive common-source outbreaks of infectious hepatitis which have been traced to contaminated water, milk and other foods. In 1955, in Sweden, alert clinicians identified through carefully taken epidemiologic histories that raw oysters were the vehicle for an epidemic of viral hepatitis. In 1961 raw oysters were incriminated in outbracks of hepatitis in Alabama and Mississippi. A second outbreak due to raw clams were identified in 1964 in Connecticut and New Jersey.

Koff *et al*[2] found that shell-fish associated infectious hepatitis can occur in sporadic as well as epidemic form. In their studies raw clams and oysters but not fried clams were consumed more often by patients than by controls. It is not surprising in view of the stability of the virus that even steamed clams though not fried clams seemed more often consumed by hepatitis patients than by controls. Obviously the usual method of preparing steamed clams by serving them when the shells gape is not sufficient to destroy the virus as Koff and Sears also showed.[3]

A significant risk of hepatitis has been recognized in animal handlers in contact with newly imported subhuman primates. It is however doubtful if the hepatitis so produced is due to the virus of hepatitis. In fact the large epidemics of hepatitis in Delhi and Ghana from simian transmission, revealed pathological changes in the liver different from that of human viral hepatitis and were probably due to adenovirus.[3,4]

A fifth type of viral hepatitis comes from transfusions and from illicit use of habituating drugs. In Koff's series seventy patients developed hepatitis following transfusions and fifteen from narcotic addiction.

Many viruses responsible for major public health problems are being brought under control by application of virological advances for production and use of preventive vaccines, but the hepatitis virus remains unconquered. We have as yet no experimental host tissue or culture system that has been found suitable for growth and propagation of these viruses, Factors in achieving unquestionable in-vitro cultivation of the agents have not been the only serious drawback to our understanding of the disease. The apparent insusceptibility of a wide range of experimental hosts to the human viruses has been a major obstruction. A promising lead pointed out by Hillis[4] is the successful transmission of viral hepatitis to marmosets. This animal is an easily handled experimental host who develops consistent changes on serial passage when inoculated with human hepatitis virus. Perhaps this will open the road to the conquest of infectious hepatitis.

In the meanwhile we must remember that the virus is amongst the most stable of all, not easily destroyed by boiling instruments, steaming clams or chlorinated water supplies. The frequency of shell-fish associated infectious hepatitis implies that this virus is common in the sewage that increasingly pollutes estuarial waters. We need to re-examine our practices and programs in shell-fish sanitation. To be safe one must avoid contact with people who have hepatitis. One must eat either thoroughly cooked shell-fish or have some warranty that the shellfish that is eaten uncooked or partially cooked came from safe waters, a very difficult order indeed.

L.H.N.

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POST

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I'm supposed to get up and do things?

With my heart?

It's entirely natural—and may even be desirable—for the cardiovascular patient to be somewhat anxious about himself.

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Cautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use may result in dependence or habituation in susceptible persons—as ex-addicts, alcoholics, severe psychoneurotics. After prolonged high dosage, drug should be withdrawn gradually to avoid possibly severe withdrawal reactions including epileptiform seizures. Side effects include drowsiness and, rarely, allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute non-thrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. Meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Warn patients of possible reduced alcohol tolerance. Should drowsiness, ataxia, or visual disturbances occur, dose should be reduced. If symptoms persist, patients should not operate vehicles or dangerous machinery. A few cases of leukopenia, usually transient, have been reported following prolonged dosage. Other blood dyscrasias—aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia—have occurred rarely, almost always in the presence of known toxic agents. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. Prescribe very cautiously for patients with suicidal tendencies. Suicidal attempts should be treated with immediate gastric lavage and appropriate supportive therapy.

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The Simple Laboratory Test

The following is reprinted by permission of the College of American Pathologists who are publishing a series of small informative leaflets entitled PathCAPsules. The subject matter is so pertinent and well stated that it seems well worth bringing to Connecticut physicians.

Is there a simple laboratory test?

If so it must be rare. Certainly many tests may seem simple if the observer or the person working at the bench is ignorant of all the pitfalls that accompany every manipulation.

As an example, let's explore hemoglobin determinations. This has been a frequently performed analysis since Gowers introduced the first method in 1878. The number of papers written on the subject since that time is astronomical. Yet just what is the present status of performance of this commonest of all tests? In 1963 a total of 398 laboratories returned results of their analyses of a hemoglobin solution.[1] Iron analyses of the sample yielded a calculated value of 15.9 Gm. of hemoglobin per 100 ml. of blood. The mean value of the returns was 15.7 Gms. Only two-thirds of the reporting laboratories obtained values between 14.9 Gm. and 16.5 Gm. Values as low as 10.5 Gm. and as high as 18.6 Gm. per 100 ml. were reported. In view of this, even though it looks simple to see a technician perform a single dilution and read the result from a scale on a photometer, it would certainly be erroneous to imply that determination of hemoglobin is a simple test.

An advertisement for Bromsulphalein (BSP) uses the provocative phrase "and is an extremely simple test to perform." This extremely simple test has resulted in a number of deaths. After eleven years experience with administering the dye it appeared to this writer that such reactions always occurred elsewhere. Amidst complacency two severe reactions were encountered following its use in one month. After such experiences would not the phrase "potentially dangerous test" seem more appropriate? According to Dr. McGath[2] who has supervised over 200,000 of these tests it is not a simple one.

Some of the potential traps in performing simple tests might be elusive to the most sagacious chemist. Even the method of transportation of the specimen to the laboratory is hazardous. The quickest way is not always the best. For example, pneumatic tube transportation of blood interferes with determinations of hemoglobin, serum LDH, and serum potassium.[3] The simple hematocrit is markedly altered when it is determined on blood taken from a vacuum tube which has been only partially filled.

What about the many "dip sticks"? In some instances, the various ribald comments overheard in the laboratory seem appropriate. In a recently published article numerous problems resulting from the estimation of blood urea nitrogen by a currently popular "simple test" are pointed out.[4] Indeed, a paradox exists when on one hand knowledge and instrumentation have shown such rapid and spectacular advances and on the other tests are offered which give imprecise and even misleading results. Moreover, hospital administrators and practicing physicians could be misled into the idea that the well appointed laboratory consists of a bag of variegated bits of paper.

If such problems are encountered in the "simple tests" the more complicated tests can be traumatic indeed for the technologist, and most hazardous to the physician and his patient. "It is high time to stop misleading the public and the physician about laboratory tests. None is simple and certainly none is extremely simple. They are all involved, complicated, and full of pitfalls and possible inaccuracies clear down to the written report on the patient's history. It takes a clear appreciation of these many possible errors and a long period of training and experience in order to master laboratory procedures to an acceptable level."[2]

The responsibility for maintaining good clinical laboratories, of necessity, resides within the medical profession. Pathologists are clearly those most responsible; however, the full understanding and cooperation of all medical groups are essential to maintaining excellent laboratory medicine standards. Indeed, it is just as important to send the patient, the patients' blood, or other biological sample to a properly supervised laboratory as it is for the patient to see a properly trained physician in the first place.

R.N.B.

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The Murder Of Wirsung

Johann Georg Wirsung described the main pancreatic duct associated with his name in 1642. One year later, on August 22, 1643, he was murdered, and this crime has been generally considered unsolved by most medical historians. For a time the murder was attributed to persons jealous of his discovery, and this legend appears in the writings of de Graaf and of Boerhaave, the latter of whom even described the murder weapon erroneously as a dagger. In a recent communication, Morgenstern[1] presents revealing information on the murder, and the murder weapon as well.

Wirsung was born in Augsburg in 1600, and spent fourteen years as one of the long line of distinguished anatomists at Padua. One of his students, Maurice Hoffman, found the pancreatic duct in an Indian rooster, and showed it to Wirsung in 1641. One year later Wirsung dissected the duct in a human, and described it in a letter to Jean Riolan, the Professor of Anatomy in the University of Paris. In the same year he published a copper print of a life size drawing of the duct.

On August 22, 1643 Wirsung was murdered, and the solution to the crime was proposed a century later by Morgagni. The latter studied the accounts of the German students at the University of Padua, and found and transcribed an entry which seemed to clarify the circumstances of Wirsung's death. On the night in question he was apparently engaging in conversation with friends at the door of his house at about midnight, when he was attacked and shot with the contemporary equivalent of a carbine by a Dr. Jacobus Cambier for personal reasons of an unknown nature. He died soon thereafter from blood loss resulting from the bullet wound. The murderer, a Dalmatian, escaped from Padua the following day in the company of a relative and another student who were considered accomplices. Morgagni concludes that the death of Wirsung resulted from a private quarrel rather than from envy at his discoveries.

H.L.

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Parenteral Tetracyclines

When a tetracycline is indicated, an oral preparation should generally be used. Tetracycline is usually effective against susceptible organisms at blood levels of 0.5 mcg to 2 mcg per ml of serum, and these levels are readily obtained with any of the oral preparations (Tetracycline Hydrochloride USP, tetracycline phosphate, oxytetracycline, chlortetracycline, and demethylchlortetracycline). A parenteral tetracycline should be resorted to only for the initial treatment of very severe infections, when the patient cannot take drugs orally, or when oral administration may be unreliable, as in a malabsorption syndrome.

Intramuscular Tetracycline—Tetracycline can be administered either intravenously or intramuscularly, but Medical Letter consultants do not favor the intramuscular route. Absorption from the intramuscular site is poor, and intramuscular administration may be followed by persistent and often severe tenderness, even when the addition of a local anesthetic to the preparation reduces the immediate pain which injected tetracycline causes.

Intravenous Tetracyclines — When a parenteral formulation is needed, the intravenous route is preferred, with administration by drop or direct injection over a period of not less than five minutes for each dose. The recommended intravenous dose of all the tetracyclines, except rolitetracycline, is 500 mg every 12 hours for adults. For infants and young children, it is 10 to 20 mg/kg/day in divided doses given every six to 12 hours.

The manufacturers of rolitetracycline (Bristol and Squibb) recommend as an adult dose 350 to 700 mg every 12 hours (Bristol does not recommend it for children). Because there has been comparatively little use of this intravenous preparation, and because of the uncertainty as to optimum dosage, The Medical Letter does not advise the choice of rolitetracycline for either adults or children.

The manufacturers of the other tetracyclines warn against the intravenous administration of more than 2 Gm daily, but Medical Letter consultants consider it safer to choose an alternative drug if more than 1 Gm of tetracycline is needed, because of the risk of severe hepatic injury; the risk is especially great in pregnant women and in patients with renal disease. Measurement of the serum concentration of the antibiotic may be necessary for adequate control of dosage.

Although liver injury has occurred with oral tetracycline, the risk is probably less than with intravenous administration; after initial emergency use of an intravenous preparation, oral administration should be started as soon as possible. (See The Medical Letter, Vol. 7, p. 69, 1965 for summary of the adverse effects of the tetracyclines. These effects can occur even with ordinary doses, oral or parenteral, and at any age; the tetracyclines can also cause fetal injury.)

Tetracyclines are eliminated mainly by way of the urinary tract; to avoid serious toxic effects, when there is considerable impairment of renal function it is important to reduce dosage whatever the route of administration. When a patient with impaired renal function requires an intravenous tetracycline, chlortetracycline may be safer than the other formulations because it is metabolized more completely (C. M. Kunin and M. Finland, Arch. Intern. Med., 104:1030, 1959). Tetracycline should never be administered intrathecally.

Brand Names of Intravenous Tetracyclines — Chlortetracycline: Aureomycin (Lederle); *oxytetracycline*: Terramycin (Pfizer); *rolitetracycline*: Syntetrin (Bristol); Velacycline (Squibb); *tetracycline hydrochloride*: Bristacycline [formerly Polycycline] (Bristol); Achromycin (Lederle); Tetracyn (Roerig); Steclin (Squibb); Panmycin (Upjohn).

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Some New Approaches To Rational Chemotherapy

Robert E. Handschumacher

■ The usual design of an introductory article is to engage the reader in the subject by extolling the achievements of the past and the outstanding qualifications of the authors of the more specialized articles. Instead, I would like to sketch for you some new developments and seek your aid in raising the level of care for patients with cancer in Connecticut by participating in their extension into clinical practice.

The certain knowledge that between one-half and two-thirds of all patients diagnosed as having cancer today will receive less than curative treatment with conventional therapy is a burden many of you have learned to accept. Some take solace in the fact that great advances have been made in our ability to make early diagnoses and thereby improve the effectiveness of surgical or radiological measures. Others will indicate that present supporting services have eased the social and economic hardships of the less fortunate individuals whose treatment is not curative. Further improvements can be expected in both of these areas and require your enthusiastic support.

Basic scientists often take justifiable pride in the remarkable expansion of our knowledge of neoplastic transformation in lower animals and to some degree in man. These efforts, however, are of little value unless a vigorous extension of these basic findings to the management of the patient is achieved. The subsequent papers will illustrate specific examples of how this is being done at the Yale-New Haven Medical Center. Equally important, these articles should serve to acquaint you with ways in which you can participate in effecting this translation of basic science into the care of patients.

What are the specific targets that can be the objective of our search for better chemotherapy in the treatment of malignancies and related hyperplasias? The early concept that cancer cells are rapidly dividing cells whose growth could be controlled by general antimitotic agents, has been demolished by the clear demonstration that many normal cells, such as those of the bone marrow, intestinal mucosa and hair follicles, have shorter generation times than many cancers. This simple concept has now been modified and current efforts are aimed at matching the period of cytotoxicity of a drug to the approximate generation time of the population of neoplastic cells; this should minimize damage to essential normal tissues whose sensitive periods of reproduction do not coincide in time or duration with those of the cancer cells. A particularly successful example of this approach is presented in studies with methotrexate by Dr. Hyrniuk and Dr. Bertino. Great potential remains for the extension of this to other agents. It must be remembered, however, that the choice of such new programs of treatment must be based on careful evaluation of the cytokinetics of the particular tumor cell population. Furthermore, the intensive periods of treatment employed can create somewhat different, though not necessarily more hazardous, reactions in the patients.

Most approaches to the design of new agents in recent years have been predicated on the assumption that the metabolism and function of nucleic acids presents the most rational target. Early success in the treatment of leukemias with the purine analog 6-mercaptopurine and related derivatives was followed by the development of 5-fluorouracil, a compound that is able to modify the chemical course of several solid tumors. Inhibition of the synthesis of deoxynucleic acid (DNA) can also be accomplished by blocking the regeneration of one of the catalytic cofactors essential to construction of the precursors of DNA. One of the most powerful agents available today, methotrexate, accomplishes this role by preventing the regeneration of the vital coenzyme dihydrofolic acid by the enzyme dihydrofolic acid reductase.

Although good results can be achieved, sufficient specificity for the neoplastic cell has not been obtained to give a manageable therapeutic index except in special circumstances. The inability to sustain response in patients who initially respond to these agents with good tumor regression is now being studied by various groups at Yale. The results of these studies are beginning to define the mechanism of resistance or tolerance. Through such an understanding specific measures are being developed either to prevent such alterations in tumor metabolism or to capitalize on them to achieve even greater sensitivity to related compounds. Examples of this may be found in the alterations during therapy in the sensitivity of the synthesis of DNA

ROBERT E. HANDSCHUMACHER, American Cancer Society Professor of Pharmacology, Department of Pharmacology, Yale University School of Medicine.

precursors to the folic antagonists detected by Dr. Bertino and his associates in leukemic cells. Another agent developed by Yale, 6-azauridine and its triacetyl derivative, possesses very little toxicity to normal tissues but during the initial phases of treatment, can produce dramatic effects on certain forms of leukemia. The improvement obtained is of very short duration and although patients can tolerate much greater doses, tumor sensitivity is lost. In this case, again we have been able to define with some precision the nature of the changes that create the refractory state, but unfortunately have not yet been able to overcome them. Future progress in these areas requires adequate numbers of patients whose condition permits the further exploration of this problem because transplantable tumors in animals generally do not exhibit the same changes in sensitivity seen in human neoplasma.

For many years, primary attention has been focused in the biochemical aspects of antimetabolites, but it has become increasingly apparent that physiological factors play equally important roles in governing responses to therapy. It is now recognized that the selective transport of certain agents such as methotrexate into cells can enhance their biochemical effect or that physiological exclusion of the agent from the central nervous system creates a sanctuary in which neoplastic cells can proliferate unaffected by the drug. To extend this concept, the antimetabolite 5-azaorotate has been developed at Yale. This compound is specifically concentrated by an active transport mechanism in the kidney and liver, and virtually excluded from other cells such as those found in the bone marrow and intestine. Such a compound might find application in the differentiated neoplasms of the liver and kidney which possess this transport mechanism, but require higher levels of nucleic acid synthesis to sustain neoplastic growth. In preliminary trials in man, the biochemical activity of this inhibitor of pyrimidine biosynthesis is consistent with its physiological properties in animals. Crystalluria and related reduction in renal function have occurred but presumably can be controlled by a good clinical management.

Since it is not always possible to direct an antimetabolite to the tumor by physiological methods, much work has been done in collaboration with surgeons to deliver the agent in high concentrations to the tumor by intra-arterial infusion. Some measure of success has been reported with treatment of localized tumors of the head and neck as well as abdominal tumors whose circulation is accessible. Rational as this may seem, there are numerous limitations to its application. What is needed is an antitumor compound that has a very short half-life in the blood but which will exert its effect primarily in the infused arterial bed. Although various derivatives of nitrogen mustard would seem to be good candidates, their use has not given outstanding results. It now seems that antimetabolites whose metabolism is very rapid such as 5-iododeoxyuridine developed at Yale by Dr. W. H. Prusoff and cytosine arabinoside offer greater promise.

It has long been an intuitive feeling among physicians that if two drugs are good by themselves, in combination they may be much better. Critical analysis of the failures and successes that result from the use of combinations of antibiotics are known to all. In the therapy of cancer, the very nature of the condition encourages, indeed at times demands, an attempt to try many drugs, often simultaneously. As a result, the literature is replete with an endless array of combination regimens whose value is virtually impossible to determine on objective grounds. It is possible, however, to design programs of combination therapy based on known physiological and biochemical mechanisms, evaluate them in experimental animals and extend the results in carefully controlled studies to human disease. Such an approach is being vigorously pursued by Dr. A. C. Sartorelli at Yale. His concepts of "complementary inhibition" are based on the premise that an attack on existing informational molecules within the cancer cell, coupled with the action of another agent which can inhibit the synthesis of new macromolecules to repair this damage, will provide a markedly synergistic effect. He has shown that combinations of uracil mustard and 6-thioguanine, whose mechanisms of action fulfill these criteria, are in fact far superior to either agent alone in reducing growth of experimental tumors and in fact can cure a significant number of animal tumors. Such results obviously deserve extension to human disease in selected patients.

Any complete approach to the problems of cancer today requires attention to the well established viral etiology of many animal tumors and the implication of these results for human disease. The principle of atomic substitution to produce antimetabolites has had outstanding success in the development of 5-iododeoxyuridine at Yale. This compound, which is an analog of the DNA constituent, thymidine, has provided the first truly effective treatment of keratitis of the eye caused by the herpes simplex virus. Experimental studies also have shown that it can prevent the induction of cancer in animals by the oncogenic viruses. When therapy of a patient with cancer has killed all existing neoplastic cells, it may still be necessary to prevent reinduction of the disease by an anti-viral agent. Exploration of this concept and the development of new anti-viral agents must occupy a high priority.

Although most efforts are directed toward a primary attack on the cancer cell, the use of chemotherapy is also being extended to provide supportive measures for the surgeon and radiologist. Perhaps the clearest illustration of this is in suppression of the immune response after homotransplantation operations. As advancements in surgical techniques afford greater opportunities for organ replacement in more radical procedures, comparable progress is demanded to limit the reaction of the host to this tissue. The elaboration of antibodies requires proliferation of competent cells and thus several antineoplastic agents have found use as immune suppressants. Work now in progress at Yale by Dr. S. Kaplan, Dr. M. Mitchell and Dr. P. Calabresi is directed toward improving these forms of treatment, particularly with judicious combinations of agents. The obvious extension of these principles to the group of autoimmune diseases is also under study. Although much is known about chemical structure and the biology of their formation and action, very few details of the actual biochemical aspects of antibody synthesis have been established. This should provide a very profitable target for antimetabolite attack and studies are beginning on this approach.

The articles contributed by Dr. R. DeConti and Dr. C. McDonald illustrate with excellent examples the manner in which pharmacological investigations, originally directed toward the therapy of cancer, are extended to other defects in metabolism or disease states. Such extensions are the consequence of an effective incisive thinking by clinicians coupled with liaison with basic researchers.

Finally, an entirely different approach to the control of leukemias and lymphomas by our group at Yale is based on what appears to be a quantitative and possibly even qualitative difference between certain cancer and normal cells. Several years ago it was reported by Dr. Kidd and Dr. Broome in New York that guinea pig serum prevented the growth of certain experimental tumors and that the active principle was the enzyme l-asparaginase. Independently, Dr. T. A. McCoy in Oklahoma and Dr. G. A. Fischer at Yale demonstrated that certain tumor cells require the amino acid asparagine for sustained growth in culture. Other neoplastic and normal cells did not have this requirement. Thus, it appears that a nutritional requirement for this amino acid exists in certain types of cells. Creation of a nutritional deficiency in this normally nonessential amino acid results in death of the sensitive cells. Other groups have begun studies of the effect of purified preparations of the enzyme asparaginase in human leukemias but insufficient results are available to make a full evaluation. Inherently this method would seem to be limited to a single treatment since an antigenic response to the foreign protein would probably follow a second treatment. Our approach has been to design an antimetabolite of the required amino acid. One of these currently under study, 5-diazo-4-oxy-norvaline inhibits the growth of asparaginase sensitive tumor lines in culture and in animals. We view this approach with considerable optimism since the target is not nucleic acid metabolism, but an apparently specialized requirement of certain neoplastic cells. A predictable consequence of this type of blockade is that it would be much less likely to cause toxicity to rapidly proliferating tissues such as the bone marrow and intestinal mucosa. The extremely low toxicity of this compound in animals confirms these predictions. Even if this analog is not successful in clinical trials, a new and exciting lead is now available that can be followed in the design of many new agents. To pursue this goal most effectively, we must probe deeper into the significance of this nutritional requirement and devise simple methods for detecting those human tumors which will by their metabolic profile be susceptible to starvation of the amino acid asparagine or blockade of its function by antimetabolites.

These few selected examples of the type of research currently in progress at Yale in the preclinical and clinical departments are intended to illustrate some developments that may mature in the near future into clinically useful modalities of therapy. The next step in this process is the most difficult. We as basic scientists are fortunate at Yale that the means are available to effect this translation through the cooperation of our clinical colleagues. The dimensions of the job are large, however, particularly in the selection and care of suitable patients in adequate numbers to do reliable studies. Our efforts can be greatly augmented by your active interest and participation in this program.

Cancer Chemotherapy: Current Capabilities

Ronald C. DeConti, M.D.

■ Contemporary Cancer Chemotherapy has made great strides since the initial clinical trial of nitrogen mustard in patients with lymphoma twenty-five years ago. In the ensuing years, vast numbers of compounds have been tested for oncolytic effects and a great many have been subjected to study in man. As individual drugs of five different classes of antineoplastic agents[1]—alkylating agents, hormones, antimetabolites, natural products and a miscellaneous group—evolved and were found to be beneficial in man, the scope of human neoplasms amenable to oncolytic therapy has continued to widen. Studies of dosage schedules and routes of administration have demonstrated variations in therapeutic response at comparable toxicity and are gradually resulting in drug regimens with improved therapeutic indices. Combination therapy comprised of agents with different biochemical mechanisms of action, given either sequentially or concomitantly, has demonstrated enhanced oncolytic effects in a number of tumors[2,3,4] and continues to be explored.

Table I summarizes the extent to which patients with advanced, widely metastatic neoplasms may currently be benefited by presently available antineoplastic agents. Such therapy is not intended to apply to primary or localized neoplastic processes which are best treated with surgery or radiation therapy. Responses are broadly categorized by the frequency, duration, and character of the antineoplastic effect expected. A complete remission is defined as one in which all clinical, laboratory or radiographic evidence of the neoplastic process has disappeared, whereas clinical improvement with some reduction in the tumor mass or the extent of involvement, but with evidence of residual disease constitutes a partial remission. The agents specified are representative of those producing the improvement, though in some instances, other agents have been employed with comparable benefit.

In a small group of tumors, the occurrence of long-term survivors in previously rapidly fatal dieases has suggested the possibility of "cure" of even widespread metastatic processes. This concept seems to have been well established for a majority of women with trophoblastic tumors as a result of treatment with methotrexate, actinomycin D and vinblastine,[5,6] and, indeed, may apply in lesser numbers to children with Burkitt's lymphoma,[7] Wilm's tumor,[8,9] or acute leukemia.[10] The remarkable contribution of cancer chemotherapy to the treatment of these childhood neoplasms has so altered the natural history of these heretofore fatal disorders that only extended observation will disclose the eventual fate of these children. In acute leukemia, at present, the best series[11] now indicates a 3.5 per cent five year survival while our overall ability to control the process, produce complete remissions and extend survival has progressed steadily as new agents have been developed and new drug schedules employed.

Complete though finite remissions are obtained frequently in a wide range of chronic myeloproliferative and lymphoproliferative disorders. These beneficial effects may often be sustained for prolonged periods and relapses may be effectively treated by appropriate alterations in drug therapy such that the quality of survival is greatly improved even in those disorders in which duration of survival is apparently unchanged.

Carcinomas as a whole respond less well to chemotherapy. Response rates are below 50 per cent even in favorable tumors; partial rather than complete remissions are the rule; and the duration of the beneficial effects achieved by a particular drug tends to be short. However, even in this group of neoplasms, improvements in survival can be demonstrated in patients exhibiting objective antitumor responses as compared with drug failures.[12,13] The availability of compounds with different mechanisms of action and without cross-resistance has increased the likelihood that an individual patient may enjoy a response and further, that the sequential use of these agents may sustain the response if drug resistance develops. This flexibility has been of demonstrable value in patients with lymphoma and is being emphasized more often in treatment of neoplasms of the breast, ovary and testis.

These accomplishments of cancer chemotherapy have demonstrated promise, that, as this scientific discipline becomes more firmly established with advances in our understanding of cellular biochemistry, tumor biology, cell kinetics, and techniques of drug evaluation, the patient with cancer will be still further benefited.

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Table I

Current Achievements of Cancer Chemotherapy

Benefit	*Disease*	*Drugs*	*Comments*
Frequent complete remissions with potential cures	Trophoblastic tumors	Methotrexate, Actinomycin D, Vinblastine	70-80% remissions, prolongation of life and probability of indefinite survivors.
	Wilm's tumor	Actinomycin D, Vincristine, Alkylating agents	Prolongation of life.
	Burkitt's lymphoma	Cyclophosphamide, Methotrexate, Vincristine	Some apparent cures.
	Acute leukemia of children	Prednisone, Vincristine, 6-Mercaptopurine Methotrexate, Cyclophosphamide	Increasing prolongation of life, with a few 5 year survivors.
Frequent complete remissions or control of neoplastic processes	Prostatic carcinoma	Estrogens, Prednisone	Prolongation of life.
	Chronic myelocytic leukemia	Busulfan, 6-Mercaptopurine, Cyclophosphamide	90% responders but increased survival doubtful.
	Chronic lymphocytic leukemia	Chlorambucil, Cyclophosphamide, Prednisone	Probable prolongation of life.
	Polycythemia vera	Busulfan, Chlorambucil	Probable prolongation of life.
	Hodgkin's disease	Alkylating agents, Vinblastine, Prednisone Ibenzmethyzin*	60-80% remissions, often prolonged with good responses to subsequent therapy.
	Mycosis fungoides	Alkylating agents, Methotrexate, 6-Azauridine*	Responses related to stage of disease.
	Lymphosarcoma	Alkylating agents, Vincristine, Prednisone	Disease often indolent, easily controlled.
Less frequent complete remissions but frequent partial remissions	Reticulum cell sarcoma	Alkylating agents, Vinblastine, Vincristine Prednisone	Remissions usually short, difficult to maintain.
	Neuroblastoma	Vincristine & Cyclophosphamide	Substantial benefit with combination therapy.
	Breast carcinoma	Estrogens, Androgens, Prednisone 5-Fluorouracil, Cyclophosphamide, Methotrexate, Vinblastine	Results with each therapy directly related to menopausal state, age, and organ involvement. Value of cytotoxic agents increasingly appreciated.
	Ovarian carcinoma	Alkylating agents, 5-Fluorouracil	40-50% responders in some series. Wide variety of agents useful.
	Multiple myeloma	Melphalan, Cyclophosphamide, Prednisone Testosterone	Marked symptomatic improvement possible.
	Endometrial carcinoma	Progestational agents	33% responders; some complete remissions.
	Head & Neck tumors	Methotrexate	New scheduling may improve frequency and duration of response.

TABLE I (Continued)

Benefit	*Disease*	*Drugs*	*Comments*
	Adrenal carcinoma	O,p'DDD	34% responders; median duration 7 months.
	Testicular tumors	Alkylating agents, Actinomycin D, Mithramycin*	Response depends on cell type. Mithramycin useful in embryonal cell carcinoma.
Partial responses less frequent or short lived	Rhabdomyosarcoma	Actinomycin D, Cyclophosphamide, Vincristine	Occasional dramatic response.
	Gastric carcinoma	5-Fluorouracil	20% responders.
	Large bowel carcinoma	5-Fluorouracil	20% responders.
	Acute leukemia of adults	6-Mercaptopurine, Prednisone, Vincristine Cyclophosphamide, Methotrexate, Cytosine Arabinoside*	Improved results with multiple drug therapy. Early data with Cytosine Arabinoside encouraging.
Benefit rare or transient	Bronchogenic carcinoma	No agent of demonstrated superiority	Largely symptomatic relief only.
	Soft tissue sarcomas	No agent of demonstrated superiority	% useful responses small, variable
	Pancreatic carcinoma	No agent of demonstrated superiority	% useful responses small, variable
	Renal carcinoma	No agent of demonstrated superiority	% useful responses small, variable
	Malignant melanoma	No agent of demonstrated superiority	% useful responses small, variable
	Carcinoma of cervix	No agent of demonstrated superiority	% useful responses small, variable

* For investigational use only.

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New Approaches To Chemotherapy Of Leukemia And Epidermoid Carcinoma

W. M. Hryniuk and J. R. Bertino

■ Leukemia, especially the acute type in adults, continues to have a dismal prognosis. Endeavors to improve treatment results have included (a) the testing of new drugs; (b) more thorough investigation of dose schedules for agents in current use; (c) use of drugs in combination and cycles;[1-6] and (d) extracorporeal irradiation.[7] The first two and especially the second of these approaches has been stimulated by the recent findings of Skipper and his colleagues[8-10] and Bruce et al.[11] These workers, using animal tumours and leukemias as model systems coupled with methods for precisely quantitating responses to different drugs and dosages, have shown that proper selection of therapy schedules can mean the difference between partial response and cure. Not only can drugs such as Methotrexate (MTX) produce cures of animal tumours but so also can certain newer analogues such as Cytosine Arabinoside, if properly used.

Taking note of these developments ,the Oncology-Chemotherapy and Hematology Units at the Yale-New Haven Medical Center, in conjunction with the Department of Pharmacology, have undertaken a re-evaluation of therapy schedules, with emphasis on one agent—methotrexate. At the same time, clinical, pharmacological and biochemical studies of several new agents, in particular, cytosine arabinoside and dichloromethotrexate, are underway. Advantage is being taken of the extensive facilities available for supportive care of the patients being studied and treated. Beneficial results are accumulating which encourage such an approach. Recent developments relating to the role of MTX in chemotherapy may serve to illustrate these concepts.

Aminopterin, a folate antogonist now supplanted by MTX, was the first antimetabolite to be applied on a rational basis and found to have a beneficial effect in the treatment of neoplastic disease in man.[12] Table I summarizes the antitumour spectrum that has evolved for folate analogues since 1949. Not listed are malignancies that occasionally respond to therapy with MTX, e.g., bladder cancer, carcinoma of the gastrointestinal tract, reticuloendothelioses, soft tissue sarcomas, etc. The point to be emphasized is that within each group of malignancies where careful systematic explorations of dose schedules have been conducted, results have been further improved, sometimes dramatically. Four examples are given below.

TABLE I
NEOPLASMS RESPONSIVE TO METHOTREXATE

NEOPLASM	RESULTS OF TREATMENT	REFERENCE
Leukemia		
Acute Lymphoblastic	30-50% complete and partial remissions	(13)
Acute Myeloblastic	10-20% complete and partial remissions	(14)
Trophoblastic Tumors	50% 5 year "cure" by Methotrexate	(15)
Breast Carcinoma	20-40% objective response	(16)
Epidermoid Carcinoma		
Head and Neck	30-50% objective response	(17-19)
Lung	30-50% objective response	(20, 21)
Burkitt's Lymphoma	20% "cure"	(22)

(1) Approximately 50 per cent of patients with trophoblastic disease can be "cured" (i.e., 5 years survival without evidence of disease) with high-dose daily treatment (20-30 mg/day x 5 days) with MTX used alone, when the drug is given in repeated courses to tolerance.[15] Since this schedule has been so effective, no comparative studies of alternate schedules have been reported. Lest it be concluded that MTX has some unique action against trophoblastic disease, it must be pointed out that Actinomycin D can by itself also cure 50 per cent of patients with the same disease.

(2) It now appears likely that some "cures" of children with Burkitt's lymphoma have been produced with MTX used in this manner whereas small daily oral doses were much less effective.[22]

(3) The advantages of high dose intermittent therapy over repeated low oral doses became especially evident from the studies of Leukemia

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Group B.[23] When MTX was used to maintain remission after initial induction, the median duration of remission was 12 weeks when the drug was given daily by mouth in small doses. In contrast, the median duration of maintained remission was 50 weeks if MTX 30 mg/M^2 was given I.M. twice weekly. Further studies have demonstrated that these large intermittent doses may be given by mouth with approximately the same results.*

(4) In carcinoma of the lung[20,21] and of the head and neck[18] large (0.8 mg/kg) doses of MTX given at 3-4 day intervals have produced clinically significant tumour regression in 30-50% of patients treated. Although these studies suggest that this dose schedule is an improvement over previously used schedules, a randomized prospective study is required to prove that these results are better than could be achieved by daily small dose oral or 5-day courses of I.V. MTX. Whereas these studies were done in patients with recurrent carcinoma not amenable to radiation therapy or surgery, several studies are now in progress that combine radiation therapy with MTX administration.[24-26] Although it is the impression that concomitant or pre-treatment with MTX of patients receiving radiation therapy increases the cure rate in drug-responsive individuals this approach has not yet been demonstrated to produce more 5 year survivors than radiation therapy alone. Attempts to improve surgical results by pre-treatment with MTX would also be worth investigating.

Leucovorin®† "Rescue"

MTX blocks the conversion of folic acid to its reduced, physiologically active forms. One of these is required for the synthesis of thymidylate, a compound pre-requisite for DNA replication prior to mitosis. Leucovorin®, a stable, reduced form of folic acid, will allow the cell to bypass the MTX-induced block if given just before, simultaneously, or soon after MTX. Several years ago Sullivan[27] first gave leucovorin® subcutaneously to patients receiving MTX intra-arterially, thus protecting against the systemic effects of the folate antagonist. It is now well established that leucovorin® does indeed protect against systemic MTX toxicity, thus allowing much more antifolate to be given intra-arterially. However, whether the same results might be accomplished by the use of small amounts of intra-arterial MTX has not yet been established.

An even more promising use for leucovorin® is based on the animal studies of Goldin et al.[28,29] If leucovorin® is administered to mice bearing I1210 leukemia *at an appropriate interval after* (12-24 hours) very large doses of MTX, MTX toxicity is prevented but the anti-leukemic activity is preserved. In fact, some animals can be cured of the leukemia by this method of therapy, since doses of MTX can be used which would otherwise be lethal for the host. Clearly this is an increase in therapeutic index.

Similar attempts to improve the therapeutic index of MTX in patients with leukemia[30] and head and neck cancer[31,32] have been initiated and show promise. In our limited studies to date, six of seven patients with acute leukemia have achieved partial or complete remission with large dose intermittent MTX therapy followed by leucovorin® "rescue."

There are obviously several questions to be raised. Why should the dosage regime be so important in determining the outcome of therapy? Furthermore, if one regime is curative in a certain proportion of cases, might not better results be obtained with yet another regime? What would be the results with "ideal" regimes in humans? How could an antidote to an antitumor agent protect the host and not the tumour from the effects of the agent? Answers to these questions are being sought eagerly, for with these answers will come new insight into the exploitable difference(s) between normal and malignant cells. It would appear, at least in animal systems, that these differential and paradoxical effects may be based on a complex interplay between the tumour, the host and the drug.

At present, at least four factors have been found to be important in understanding the action of chemotherapeutic drugs, in addition to the biochemical mode of action: (a) the proportion of the total population of malignant vs. host cells entering different stages of the cell cycle i.e., G_1, S, G_2, M,* for any selected time span, and the duration of each of these stages; (b) the part of the cell cycle during which a given drug is most injurious to a cell (normal or malignant); (c) the dose of the drug required to achieve maximum (minimum) effect on each susceptible malignant (normal) cell; (d) the duration for which this dose must be administered to achieve maximum (minimum) exposure to the population of malignant (normal) cells. From a detailed knowledge of these factors in animal systems, it becomes possible to predict the requirements for, and then to achieve a cure of, the malignant disease and be left with a normal animal. In humans at present no such model can be constructed for lack of detailed knowledge of most of these variables since reliable techniques for obtaining this information are not available.

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* J. Holland, personal communication.

† folinic acid, Lederle

* The different stages of the cell cycles are defined as follows:

M = mitosis.

G_1 = period after mitosis but before DNA synthesis can be detected.

S = period during which the cell synthesizes DNA, in preparation for mitosis.

G_2 = period following completion of DNA synthesis but before mitosis is initiated.

Methotrexate is unique among the clinically useful antitumour agents. Not only is there a specific antidote for clinical and experimental use but its biochemical mechanism of action is most fully (though not completely) understood and exquisitely sensitive and accurate assay methods for its actual presence in and effects on tissue have been worked out.[33,34] Thus apart from its proven antitumor activity and spectrum, it affords a unique tool to explore some of the basic aspects of human malignant disease alluded to above. In this sense, intensive study of individual patients receiving the drug in new regimens compliments the large-scale clinical studies of these same regimes.

For example, studies currently in progress indicate that for a given dose of the drug *in vitro*, effects of MTX on human leukemia cells can be correlated well with the subsequent *in vivo* effects on the same leukemia cells—not only in biochemical but also in clinical terms. Thus in sensitive cells the target enzyme* is blocked and the cells cannot synthesize DNA *in vitro* in the presence of the appropriate level of MTX whereas resistant cells can. The same level of MTX achieved in the patient produces the same result—i.e., the synthesis of DNA in cells harvested during therapy is either blocked (sensitive) or not (resistant) or partially blocked (partial response). Furthermore, these effects correctly predict whether or not the leukemia will respond clinically to the drug, at least on a short term basis.

Obviously, these tests, if they prove reliable, may have several benefits:

(1) the capability to precisely predict responsiveness to therapy at different doses—this would confer great advantage to the chemotherapist beforehand.

(2) the potential to rationally alter the regime during treatment to continuously obtain maximum effect within the bounds imposed by toxicity (reversed or prevented by leucovorin®).

(3) the opportunity to study human leukemia in serial fashion to detect the presence of and the basis for resistance to an antimetabolite at the biochemical level in humans. This has so far eluded workers in cancer research and treatment.

New Drugs

Two new compounds are being evaluated for anti-leukemic activity at this medical center, cytosine arabinoside and dichloromethotrexate. The latter drug has received limited clinical trials, based on very encouraging results obtained in the L1210 murine leukemia screen.[35] Unlike methotrexate, this drug is extensively metabolized in man, primarily by a liver enzyme called aldehyde oxidase;[36] therefore, this drug may possess advantages over methotrexate for intrathecal, intra-arterial and intra-cavitary administration. For example, when patients with hepatomas are infused with this drug via the hepatic artery, the normal liver can inactivate the drug while the hepatoma may not be able to carry out this detoxification and thus be exposed to high levels of active antimetabolite.

Cytosine arabinoside, a cytosine analog, has been shown to possess activity in acute myelogenous leukemia in adults, as well as in children with acute lymphatic leukemia, refractory to conventional therapies.[37,38] Investigations of the mode of action of this drug at the biochemical level, as well as an evaluation of new dosage schedules and drug combinations are in progress. These early results have been most encouraging, and this new chemotherapeutic agent promises to be a valuable new agent in the treatment of leukemia.

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* dihydrofolate reductase.

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Antitumor Drugs In Diseases Of The Skin

Charles J. McDonald, M.D.

■ The treatment of skin diseases with chemotherapeutic agents, designed primarily for the treatment of malignant visceral disease, is not entirely new. Yet, only in the last 10 years has there been a genuine interest demonstrated by clinical pharmacologists and dermatologists in those chemotherapeutic agents having chemical properties which make them especially useful in the therapy of proliferative (benign or malignant), viral and autoimmune diseases of the skin.[1-4]

The following discussion will be limited to two dermatologic diseases and the chemotherapeutic agents used to treat those diseases. Psoriasis is an example of a benign proliferative disorder of the skin that is treatable with cancer chemotherapeutic agents. Mycosis fungoides is an example of a malignant disease of the lympho-reticular system that affects the skin primarily, and can be treated with moderate degrees of success using the same chemotherapeutic agents.

Psoriasis

Description: Psoriasis is a chronic, occasionally acute, inflammatory disease of the skin that affects about 3% of the population of this country. The skin eruption is usually symmetrical and has a predilection for the extensor surfaces of the extremities, especially about the elbows and knees. The scalp, nails, genitals and other body areas are often involved. The typical lesion is a red-brown, flat papule or circumscribed plaque of variable size that is slightly infiltrated and covered with silvery-white, imbricated scales. In most patients psoriasis remains limited to several coin sized areas scattered over the body. However, in a fairly large number of patients the disease is quite extensive, and in some it may involve the entire body surface. Psoriasis tends to have seasonal recurrences, and like many other diseases of the skin may be influenced by emotional trauma.

In 15 to 20% of patients with psoriasis there is an associated polyarticular arthritis. The small joints of the hands and feet are most often involved; this is particularly true of the distal interphalangeal joints. In a significant number of patients, larger joints of the cervical spine, sacrum, and shoulder and pelvic girdles may be affected. As the arthritis progresses with time severe joint deformities occur. The skin and joint manifestations, singly, or in combination are often severe enough to cause crippling and complete debilitation of the patient.

Investigations by Van Scott and Ekel have demonstrated that psoriasis, in addition to being an inflammatory disease, is also a disease characterized by cellular hyperplasia.[5] There is evidence of an increase in the mitotic activity of epidermal cells, and a reduction in epidermal cell transit time, i.e., the amount of time required by an epidermal cell to travel from the region of the basal cell layer to the keratinized layer of cells in the epidermis.

Treatment: *Local.* Therapy for psoriasis is quite variable, and it must be individualized. The disease may remit as a result of therapy; often it will disappear spontaneously. However, in most cases frequent recurrence is a definite probability. In mild cases, applications of topical corticosteroids or tar preparations are sufficient to control the disease. In moderately severe cases, twice daily applications of tar and controlled exposure to ultraviolet light often cause a remission of disease. In the severe, non-responsive cases other methods of therapy may be required, as soft x-rays and antimetabolites.

Antimetabolites. In 1953 a small group of dermatologists began using the folic acid antagonist aminopterin in severe recalcitrant forms of psoriasis.[13] As would be expected, toxic reactions were observed in a large percentage of patients. However, large numbers of deaths as rumored, were not recorded. In fact, two of four deaths reported in the literature were not directly related to drug therapy, but were probably related to associated disease states.[6,7]

In 1958, Edmundson and Guy used methotrexate (amethopterin) instead of aminopterin, believing that the therapeutic index of methotrexate was much greater.[8] In early 1964 Van Scott and Auerbach described an intravenous technique using methotrexate in severe psoriasis.[9] Also, in 1964, Turner and Calabresi described preliminary observations using the orotidylate decarboxylase inhibitor triacetyl-6-azauridine.[10]

What is the rationale for the use of antimetabolites in the treatment of psoriasis? Antimetabolic drugs are drugs that inhibit nucleotide synthesis.

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All living mammalian cells require nucleoprotein for the transmission of hereditary factors, and for cell growth and reproduction. Any abnormality in the mechanism of nucleoprotein formation is followed by alterations in cell growth and reproduction. Nucleic acids are the primary constituents of nucleoprotein, and are formed either through the *de novo* synthesis of purine and pyrimidine nucleotides, or through the intracellular formation of purine and pyrimidine nucleotides from performed purine and pyrimidine bases. Cells from malignant neoplasms and psoriatic epidermis require large quantities of nucleoprotein. Oral and gastrointestinal mucosa, hair matrix and normal bone marrow also require large quantities of nucleoprotein. Cells in the normal tissues and in the disease states above are required to synthesize the huge quantities of nucleotides needed for use in nucleic acid formation. It is observed that these cells both normal and abnormal are most sensitive to anti-metabolic drugs.

Methotrexate (amethopterin). In the *de novo* synthesis of purines, tetra-hydrofolic acid acts as a donor of one carbon units to the purine base ring structure. Tetrahydrofolic acid is formed from the reduction of folic acid, by the enzyme folate reductase. Methotrexate competitively inhibits this reaction.[11] Folate reductase has an affinity for methotrexate which approximates 100,000 times its affinity for folic acid. Hence, methotrexate combines with all of the available folate reductase in the cell leaving none to catalize the conversion of folic acid to tetrahydrofolic acid. There results a concomitant reduction in purine nucleotide synthesis. In the biosynthesis of the pyrimidine nucleotide thymidilic acid from uridylic acid, one carbon unit transfer is also mediated by tetrahydrofolic acid.

Methotrexate may be given parenterally or by mouth. When taken orally it is absorbed erratically and incompletely. Oral absorption is related to the dosage of drug administered and the status of the gastrointestinal mucosa. Prolonged periods of drug administration cause changes in the gastrointestinal mucosa which may lead to abnormalities in drug absorption. Orally administered methotrexate is absorbed slowly and excreted slowly thereby prolonging the period of contact between cell and drug, thus increasing the toxic manifestations of the drug. There are no absorption difficulties associated with parenteral drug administration.

Methotrexate excretion depends primarily on the amount of drug administered, the route of administration and the kidney function status. A large dose of drug, given orally or parenterally, is excreted mostly unchanged by the kidneys. 85% of an intravenous dose is excreted in the urine 6 hours later, whereas twelve hours is necessary for the similar recovery of an orally administered dose of drug. The remaining 15% is excreted sometime later, mostly in the feces. Methotrexate is not known to be incorporated into cellular constituents.

Drug toxicity is manifest by tissues which are characterized by high rates of mitotic activity and correspondingly elevated rates of metabolism, such as bone marrow, oral and gastrointestinal mucosa, and hair matrix. Bone marrow toxicity is particularly important and is probably the major limiting factor in the use of metustrexate. It is manifest by a drop in the peripheral white count 4 to 7 days after the drug is given, a drop in the reticulocyte count in two to seven days, and a reduction in the platelet count five to twelve days after drug administration. When oral mucosal lesions occur, they appear to be a result of an inhibition of mitotic activity and of cellular replication without replacement of rapidly desquamated cells. Studies of cell kinetics in the oral cavity and upper gastrointestinal mucosa in man indicate a cell turnover time which approximates that of psoriatic epidermis. The measured replication rate of the hair matrix is about 24 hours. Four to five days after a single large dose of methotrexate, the hair bulb on histologic examination looks markedly atrophic. In the absence of a second immediate insult there is a rapid resumption of normal hair growth. If the insult is severe or is rapidly repetitive, a marked constriction will appear in the hair shaft corresponding to the time of the insult, or complete cessation of hair growth at the hair matrix will occur. Temporary alopecia can result from fracture of the hair shaft at the constriction or from the complete cessation of hair growth in the hair matrix.

Other toxic effects of methotrexate have been reported; most have been poorly documented. These have included transitory rises in BSP retention and transitory elevations in SGOT levels.[12] One case of periportal fibrosis of the liver, similar to that observed in children with acute leukemia given methotrexate, has been reported, however, this case was poorly documented.[13] Many deaths have been rumored in psoriatic patients given methotrexate therapy; few have been reported.[6,7] Death has been attributed to gastrointestinal bleeding secondary to ulceration of the gastrointestinal tract, and to complete bone marrow suppression with subsequent overwhelming bacterial infection. Most, if not all, of these complications have occurred in patients given oral or parenteral medication at dosage levels that were too large or given for too long a period of time without adequate supervision. All toxic manifestations are usually reversible when drug therapy is terminated.

To reduce the number of complications, patients treated in the psoriasis chemotherapy clinic of the Yale-New Haven Medical Center, are given complete hematologic, hepatic and genitourinary examinations prior to institution of therapy. Patients found to have a compromise of either of these systems are treated accordingly. It is most important that patients treated with methotrexate have good renal function, because the major portion of an administered dose of drug is excreted via the kidneys. Prior to the administration of each parenteral dose of drug a white blood count is taken. Any patient showing signs and symptoms of infection or having abnormally low white blood counts are omitted from treatment. Liver and renal function studies are repeated at appropriate intervals. Patients on oral therapy are given no more than a two week supply of drug. Parenteral drug is given at intervals and in amounts sufficient to keep the patient comfortable and functioning at or near normal capacity. These precautions have kept the incidence of drug toxicity to an absolute minimum.

6-azauridine. The development of 6-azauridine as a potential agent for the therapy of neoplastic diseases in man culminated approximately 7 years of fundamental research in the Laboratories of Pharmacology at Yale University and the Organic and Biochemical Institute in Prague, Czechoslovakia.[14] The same number of years have been spent in clinical investigations of this drug.

The principal action of 6 azauridine in mammalian systems is the intracellular inhibition of pyrimidine nucleotide synthesis. The specific site of the inhibition is the enzyme, orotidylate decarboxylase, which forms uridylic acid from the ribonucleotide of orotic acid in the *de novo* pyrimidine biosynthetic pathway.[15] The metabolically formed 5′ phosphate of 6-azauridine, i.e., azauridylic acid, competitively limits the access of the normal substrate orotidylic acid to this enzyme. This inhibition in turn inhibits the synthesis of nucleic acids.

Azauridine when administered orally as the triacetyl form is rapidly absorbed from the gastrointestinal tract. 80% of an orally administered dose is converted by the gastrointestinal mucosa to the active form 6-azauridine. 15% is absorbed and excreted as the monoacetyl form, and 5% is absorbed and excreted as the unchanged triacetyl form.[16] 95% of an orally administered dose is excreted 8 hours after ingestion; the remainder is excreted over a 24 to 48 hour period. The drug does not accumulate appreciably in body tissues.

Triacetyl-6-azauridine has relatively few toxic manifestations. Leucopenia, thrombocytopenia, hair loss, gastrointestinal symptoms, and oral aphthous ulcerations are not manifestations of 6-azauridine toxicity. Liver and kidney function abnormalities have not been detected. The most common toxic manifestation observed to date is a mild to moderate reduction in hematocrit and red cell count that is alleviated by cessation of therapy or reduction in drug dosage. Very infrequently, patients manifest signs and symptoms of central nervous system toxicity. They may exhibit drowsiness, myoclonic movements of the extremities and hyperreflexia. Neurotoxicity is thought to be related to the presence of small quantities of azauricil, a known neurotoxin, in the imperfectly purified drug. Intravenous administration of pure 6-azauridine in the same patient eliminates the presence of azauricil, and eliminates almost immediately signs and symptoms of neurotoxicity. In several patients who have apparently devoloped a tolerance to neurotoxicity, reinstitution of 6-azauridine therapy after a 5 to 7 day period of abstinence, has not been accompanied by the reappearance of neurotoxic manifestations.

Results of Treatment: Methotrexate produces clinical improvement in approximately 80% of treated patients; about 40% will have complete remission of disease. Most improvements or remissions last only as long as drug is given; termination of therapy usually results in return of disease. Arthritic deformities cannot be corrected with chemotherapy, however progression of arthritic disease is usually halted. X-ray examination of involved structures will at times show recalcification of previously osteoporotic bones.

The experience with triacetyl-6-azauridine in psoriasis in this country to date has been limited to the Chemotherapy Section of the Departments of Medicine and Pharmacology, Yale University School of Medicine. Thirty-three patients have been treated with triacetyl-6-azauridine. Complete remission of disease has been observed in over 50% of treated patients. Good to excellent clinical response has been noted in over 95%. (See figs. I, II). Patients having all forms of psoriasis have been treated with triacetyl-6-azauridine; this includes recalcitrant pustular psoriasis, and psoriatic erythrodema. Only 1 patient has failed to respond.[17] Forty per cent of the 33 patients have previously been treated unsuccessfully with other antimetabolities. The drug is not yet produced for commercial use. It is anticipated that at the completion of several current clinical studies, sufficient data will have been accumulated to satisfy present government regulations necessary for commercial distribution of triacetyl-6-azauridine.

Mycosis Fungoides

Description: Mycosis fungoides, although designated a separate disease entity by Alibert in 1806,[18] remains a variously defined and poorly understood clinical entity. Early descriptions of the disease considered primarily the cutaneous features. It is now generally agreed that mycosis fungoides is a neoplastic disease of the lympho-reticular system involving the skin and visceral organs. Cutan-

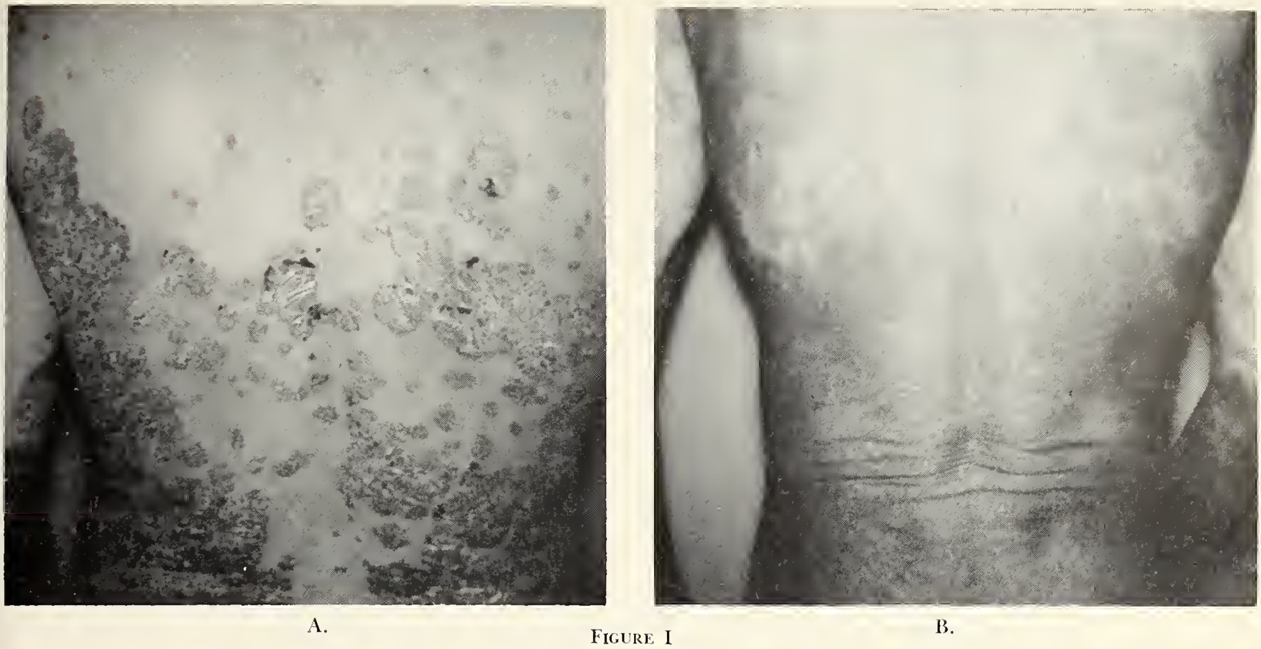

A. B.

FIGURE I

A 60 year old male with extensive plaque type of psoriasis. Experienced minimal response to oral and parenteral Methotrexate. A. Before treatment with oral triacetyl-6-azauridine. B. After 6 weeks of oral triacetyl-6-azauridine therapy, only post-inflammatory hyperpigmentation remains.

eous erruptions are present in all cases of the disease, visceral lesions occur in 40-50% of cases. These visceral lesions rather than cutaneous eruptions may often be the immediate cause of death. Skin eruptions vary in appearance from a non-specific dermatitis to obvious skin tumors. The initial skin lesions may last from 6 months to 40 years. Three clinical stages of the disease are recognized based on the clinical appearance of skin lesions. These stages are significant prognostically as well as therapeutically, and may occur singly or in combination. Stage 1, the eczematous or erythematous premycotic stage is the least malignant of the three stages, prognosis is relatively good and therapy is often quite rewarding; this stage is compatable with longevity. Stage 2, the infiltrated plaque stage is usually followed by stage 3, the tumorous and ulcerative stage. Long lasting therapeutic remissions are less likely to occur in the latter two stages. Death is often rapid after the onset of stage 3.

Lymphadenopathy is a very common clinical finding.[19] Histopathologic examination of an enlarged lymph node may reveal a non-specific cellular infiltrate, the so-called dermatopathic lymph node; it may show a polymorphous cellular infiltrate typical of mycosis fungoides, or it may have the appearance of a lymphomatous lymph node. The liver, spleen, heart, lungs, kidneys and other visceral organs may also be involved.

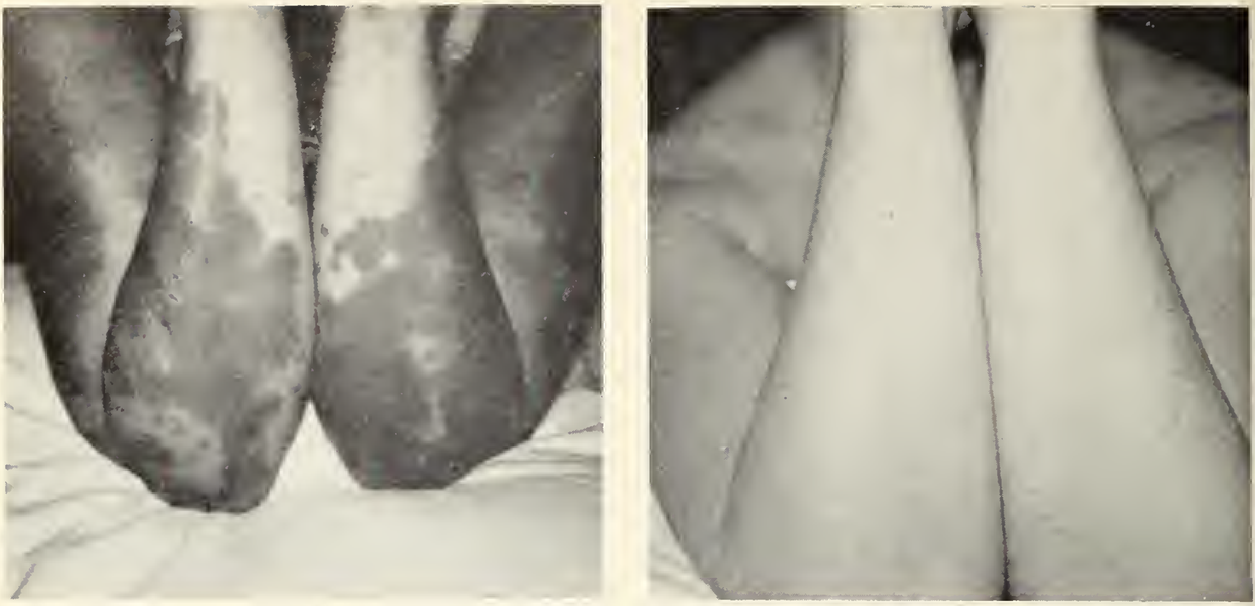
Abnormal hematologic findings include eosinophilia, anemia and leucocytosis. Abnormal lymphoid cells may be seen in the peripheral blood or bone marrow. Mycosis fungoides has been known to transist into lymphoma, either reticulum cell sarcoma, lymphosarcoma or Hodgkin's disease. Lymphomatous disease terminating in leukemia is a rare occurrence.[20]

Treatment: The therapy of mycosis fungoides like that of leukemia and lymphoma is palliative. Topical and systemic corticosteroids and alkylating agents have been used with minimal success except in isolated cases. Electron beam therapy, has been most successful in alleviating the skin manifestations of this disease. The most successful chemotherapeutic results have been obtained with the antimetabolites, methotrexate[21] and triacetyl-6-azauridine.[17] We have treated a total of 6 patients using triacetyl-6-azauridine. Five have had satisfactory responses to therapy. Best results have been obtained in patients with stage 1 and 2 disease. This is comparable to the experiences noted with other antimetabolites and electron beam therapy.

The rationale and regimens for use of these drugs in mycosis fungoides are very similar to those used in the management of severe psoriasis. The same precautions, in regard to methods of drug administration, and the status of renal, hepatic and hematopoietic systems, are taken when treating mycosis fungoides. However, because this is a malignant disease treatment may be pursued with greater intensity. Toxicity is the same as that observed in patient administered the same drug for psoriasis.

Summary

This discussion has summarized the use of two antimetabolic drugs, the pyrimidine analogue, 6-



A.

B.

Figure 11

A 46 year old female with severe psoriasis was unresponsive to weekly parenteral doses of 100 mg. Methotrexate. A. Before oral triacetyl-6-azauridine therapy. B. 5 months after initiation of oral triacetyl-6-azauridine.

azauridine, and the folic acid analogue, methotrexate, in the treatment of a benign proliferative disease of the skin, psoriasis, and a malignant disease of the lymphoreticular system whose major manifestation is in the skin. It is unnecessary to defend the use of either drug in the treatment of mycosis fungoides. However, to those unfamiliar with the various manifestations of a benign skin disease such as psoriasis, this form of therapy probably necessitates a defense. One has only to see an individual, previously physically and emotionally handicapped by psoriasis and psoriatic arthritis, return to a useful role in life, to be convinced of the necessity for use of these drugs. The use of antimetabolites in severe psoriasis has been accepted as a standard form of therapy by most dermatologists. They also agree that this form of therapy is not without danger and should be carried out by one who is totally familiar with the drug being used, i.e., its complete intracellular metabolic pathways, its absorption and excretion, and its toxic manifestations.

It should be reemphasized that antimetabolite therapy in psoriasis is to be reserved for patients with severe skin or joint disease not responsive to conventional forms of therapy.

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ESTABLISHMENT OF A REGIONAL CENTER FOR ADULT LEUKEMIA AT YALE-NEW HAVEN MEDICAL CENTER

The hope for the eventual control and possible cure for cancer is research. Leukemia, especially the acute variety in adults, as a prototype for malignant growth, is an important key to the understanding of the neoplastic process. The Cancer Chemotherapy and Oncology Section and the Hematology Section of the Departments of Medicine and Pharmacology of the Yale University School of Medicine is engaged in an intensive study of the clinical and biochemical effects of antimetabolites in patients with acute leukemia. It is recognized that such patients require extensive supportive care, and will receive the benefit of close supervision, not only by the members of the sections mentioned, but also by consultants in other specialties, in particular, infectious diseases. Patients will be hospitalized at no expense to themselves in the Clinical Research Center or in a regular medical ward, depending on the patient's condition and the purpose of the study.

Physicians are invited to refer such patients, with or without prior treatment, for evaluation and possible treatment with modified dosage schedules of conventional therapies and with promising new agents.

Patient referrals may be made by contacting one of the following:

Dr. Joseph R. Bertino—562-1161, Ext. 2301
Dr. Ronald C. DeConti—562-1161, Ext. 2301
Dr. Stuart C. Finch—561-1161, Ext. 2681
Dr. Pasquale E. Perillie—562-1161, Ext. 2681

Cancer Chemotherapy In The Community Hospital

Marvin L. Hoovis, M.D.

The steady increase in the usefulness of chemotherapy has significantly changed our approach to the treatment of patients with neoplastic diseases. The complexities of initial diagnosis, treatment and after-care have come to involve many organizations within the community. The physician is concerned primarily with the problems related to diagnosis and general management. The hospital offers its facilities for both diagnostic and therapeutic measures. With increasing emphasis on the application of palliative measures, many patients with metastatic neoplastic diseases may now receive treatment at a local level with the community hospital playing a central role. In a majority of these patients, extension of tumor or metastatic tumor will no longer be amenable to additional surgery or radiation therapy. This particular group of patients would most benefit from a well organized chemotherapy program.

Four important factors must be stressed to clarify this type of program. The first is an appreciation of the benefits that are possible utilizing the chemotherapeutic agents that are available and their relative value in specific diseases. This is discussed elsewhere in this special issue and in many other reviews of advancements in therapy.[1-3] Second is the function of the chemotherapist within the community and his relationship to the community hospital. Third is the integration of the community hospital with community services for the overall care of the cancer patient. And fourth, a practical organizational schema for the effective integration of chemotherapy into an oncology service in the community hospital.

An understanding of the concepts of the use of chemotherapy is important in defining the role of the chemotherapist. Karnofsky[4] separates the investigational chemotherapist oriented to research and development of new drugs, various drug schedules and studies of different methods of administration, from the applied or clinical chemotherapist who follows treatment schedules of previously established value and is familiar with the overall problems of oncology in addition to the uses of specific chemotherapeutic agents. This does not imply that there is a complete separation with no common meeting ground, but rather that a close association of these two areas is necessary to coordinate treatment, report drug evaluations and to develop an improved cancer therapy program.

Much of current knowledge and experience derives from the efforts of basic scientists engaged in studies of neoplastic diseases in animals. These investigators have performed countless, meticulous studies in order to determine the best methods of administration of specific drugs for neoplastic diseases. The route of administration—oral, intramuscular, rapid intravenous or proloned infusion—has now been shown to be as important as is the length of a given course of therapy and the treatment interval. Through the painstaking efforts of these individuals, we have derived many valuable drug protocols which have increased the benefits of chemotherapeutic agents in specific neoplastic diseases; biochemists and pharmacologists have contributed much to our knowledge of the specific action of drugs within the cell, the mechanisms of action of various drugs and most important, have clearly shown the problems relative to drug toxicity. All of these investigators continue to play an important role in the development of newer drugs which will eventually, we hope, effectively control cancer and other neoplasms. One must adequately stress the importance of this basic research and the retention of the essential features of these programs in our continuing efforts to understand better the mechanism of action of our present drugs as well as creating newer and more effective drugs. As practicing physicians, we must wholeheartedly support this research in order to achieve our ultimate goal which clearly must be the eradication of cancer and other neoplastic diseases. I feel strongly that we should continue to support these investigators engaged in cancer research and offer them the full cooperation of the entire medical community.

While it is not difficult to appreciate fully the importance of the basic research program and its ultimate benefits, we must still face a major problem which, expressed in simple terms, is "what do we do for TODAY'S patient with a neoplasm which is beyond the stage of further management with either surgery or radiation therapy." It is for the benefit of this particular group of patients that we must fully utilize the knowledge, facilities and the therapeutic modalities available including antineoplastic agents in an attempt to achieve long term

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remissions, partial responses or, in unresponsive tumors, at least to eliminate the agony of pain which may accompany many of these neoplasms. We must endeavor whenever possible to establish an exact histopathological diagnosis of each tumor, its extent of local and/or regional spread, the specific areas of involvement with metastases and to establish if other organs or glands are involved with a specific primary tumor. Many of these factors can now be evaluated through the use of refined diagnostic techniques. Once we have established the diagnosis and have then performed the important adjunctive studies, we then attempt to utilize in a rational way the specific chemotherapeutic agent or agents which offer the best possible hope of remission or palliation and in rare cases, "cure." Certainly, it is in this particular area of cancer therapy that the clinical chemotherapist can assume an important role.

The clinical chemotherapist should be well disciplined in all aspects of conventional drug treatment, he should be familiar with the current chemotherapy literature, he should have an affiliation with the investigators in basic research programs, he should have a thorough knowledge of the biochemical and pharmacological principles relative to drug therapy and most importantly, he should impart his knowledge and experience for the benefit of the total oncology program in a community hospital. Clinical chemotherapists must be aware of the many facets in a given cancer from diagnosis through recurrence and the progression to advanced stages with particular emphasis on treatable complications—i.e. adrenal gland insufficiency or hypercalcemia. One must stress the need for careful records including drug or drugs used in therapy, route of administration, frequency of course of therapy and of utmost importance, evidence of toxicity in every patient with metastatic neoplastic disease. With careful studies and appropriate records available for evaluation by both the investigational and the clinical chemotherapist, it will be possible to establish the value of single agents or combination of agents in specific neoplasms.

The stress on early diagnosis and treatment of cancer retains a role of importance; however, in spite of our efforts, we continue to face the problem of treating the patient with far advanced cancer with means of chemotherapeutic agents. Until recently, the regional medical center played a unique role in the management of patients with neoplastic diseases, because it offered excellent treatment and diagnostic facilities not available elsewhere. These facilities have since been burdened with the increased number of patients being referred for treatment and diagnosis. With the proven value of chemotherapy in specific neoplams and the increasing availability of chemotherapists in the community hospitals, it will no longer be necessary for all patients with malignancies to receive treatment at a regional medical center. It is hoped that many patients will eventually benefit from a carefully organized oncology program at a local level within the framework of the community hospital. This type of community program approach would do best to encourage the use of conventional drug protocols undertaken by chemotherapists familiar with drug dosages, toxicities and other limiting factors, i.e., such as the platelet deficiencies and/or bleeding problems in acute leukemias. The regional medical center would retain its position as the keystone of treatment and would be utilized for consultations in cases where the diagnosis or proposed therapy is not clear. Some patients may benefit from early referral for complete care to the medical center and in these instances follow-up reports should be made available to the referring physician. If this type of program can be initiated, it will encourage a free flow of ideas, it can also permit the investigators to have access to patients with specific diseases or interesting associated problems so that good controlled drug studies may be performed and result in useful data.

The community hospital must have certain efficiency standards in addition to the necessary personnel and diagnostic facilities important in establishing a successful oncology program. To initiate this program, the availability of the clinical oncologist and chemotherapists qualified in recognizing the various aspects of general cancer management are of primary importance. The role of the pathologists would certainly be most important because without any doubt, the basis of all tumor management rests with the establishment of the tissue diagnosis. Closely related to the pathologist is the laboratory which is under his jurisdiction. The laboratory should offer quality control of the specific tests necessary to evaluate the effect of the chemotherapeutic agents on the blood and other tissues. The surgeons play a dominant role in the management of cancer. They obtain the initial tissue specimens so vital in determining the necessary course of therapy, and perform curative cancer surgery as well as the necessary palliative surgical procedures, i.e., relief of obstruction. The neurosurgeons provide relief of pain with alcohol blocks, rhizotomies, cordotomies and section of cranial nerves. The radiologists are essential for their diagnostic and therapeutic contributions in neoplastic diseases. The availability of cobalt therapy and isotope diagnostic studies plays an important role and should be integrated equally with other forms of therapy available. The hematologists would certainly be welcomed for the assistance they offer with the specialized problems of the blood dyscrasias.

Needless to say, but of considerable importance, the assistance of all the medical and surgical specialities will strengthen any oncology program and will add important advantages in the care of patients burdened with neo-diseases. While not as essential, there are many other services available in the community hospital which can be beneficial to the patient. The biochemist and cytotechnologist will play increasing roles in cancer management and diagnosis. The Department of Physical Medicine can assist in various phases of rehabilitation with facilities for proper fitting and training in the use of prostheses. Another important area within the community hospital which offers help is the Social Service Department where many request for adjunctive services and aids can be initiated.

After discussing the many ideas and proposals necessary in relating the role of the hospital and its personnel in the care of the cancer patient, one important question remains to be answered. . . . "What benefits are available to the patient under this type of program?". Frequently, the patient with an inoperable tumor will become a community problem. Our task is to resolve some of the problems these patients must face and offer them additional relief. First and probably most important in this program, the patient could remain in a familiar environment and may be spared the oft times arduous task of travels to distant places. The problems of commuting long distances and, in some cases when no longer able to travel, having to be hospitalized in a distant city could be resolved. The psychological advantage inherent in having the patient at home or close to home certainly is apparent. Treatment at a local level can be offered within the framework of a well organized community hospital oncology program. This would also offer the family of the patient an opportunity to be near and offer their encouragement. The close proximity of the hospital's laboratory and radiodiagnostic facilities would encourage the utilization of these facilities when necessary. Secondly, the referring or family physician may actively participate in the overall management of his patient and provide continuing care. Finally, and of extreme importance, are the many community services available at the local level. Those physicians involved with the treatment of advanced neoplastic diseases appreciate the complexities of the problems of each individual patient and are fully aware of the assistance available from the local community services. As mentioned previously, the most integral part of this care may originate in the hospital under the direction of the Social Service Department. Many of these programs require long range planning and involve matters of placement or finances but these problems are handled capably by the Social Service workers. Arranging for the appropriate domestic help, convalescent facilities, home care and visiting nurses are only part of the many services available. Other aspects of community services are equally important and are usually carried out by volunteer service organizations. The Red Cross has been helpful in arranging for transportation to the tumor clinics, for laboratory and x-ray examinations in addition to its Blood Bank program. Although present at national and statewide levels, the American Cancer Society and the Leukemia Societies provide their greatest assistance to individual patients at the local level. The society member can offer more help with a thorough knowledge of the patients specific problems. In addition to their financial aid specifically to the patient, the American Cancer Society provides support for many educational programs made available to the public and also plays an important role in obtaining grants for purposes of research and/or equipment.

With the careful evaluation of each individual patient's symptoms, pathological diagnosis, previous

SCHEMA FOR A CHEMOTHERAPY SERVICE IN A COMMUNITY HOSPITAL

Purpose: To aid in the management of all neoplastic diseases where oncolytic agents are indicated.

Function:

1. To establish and maintain an active chemotherapy section, the membership of which is to be composed of physicians experienced in the treatment with chemotherapeutic agents.
2. Members to provide consultation services, for both ward and private patients.
3. Organization and staffing of a chemotherapy clinic.
   a. Follow-up chemotherapy of all ward patients
   b. Evaluation of ward patients referred for chemotherapy
   c. Training of house staff
4. Coordination with the departments of medicine, surgery, pathology and radiology in treatment of malignancy.
5. Coordination with the graduate training program.
   a. Active participation with members of the house staff.
   b. Review of patients made available by their physicians.
   c. Review advances in cancer chemotherapy at regular intervals.
   d. Members to participate in weekly Oncology Consultation Clinic.
   e. Regular meetings with members of the regional medical center chemotherapy section (Yale).
6. Affiliation with chemotherapy section of a regional medical center (Yale).
   a. Referrals of special problems for diagnosis and/or therapy.
   b. Continuing education program with active participation.

therapy and present status clarified by all available diagnostic techniques, the treatment with a well organized chemotherapy program within the community hospital will offer the greatest benefits to patients with advanced neoplastic disease.

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Combination Chemotherapy In Clinical Practice: Recent Applications To Gynecologic Cancers

Maclyn E. Wade, M.D. and Henry M. Williams, M.D.

■ The successful application of multiple drug regimens to clinical cancer has recently stimulated great interest in combination chemotherapy. The rationale for such an approach to neoplastic disease stems from "the multiplicity of alternate biosynthetic pathways possessed by the neoplastic cell (which)—reduces the importance of any single enzyme block;—thus a multipronged attack on a metabolic area may prove advantageous."[1]

Heretofore, combination chemotherapy has been employed chiefly in the treatment of acute childhood leukemia. There have been encouraging results, however, in solid tumor therapy as well, particularly gynecologic malignancy. The purpose of this paper is to emphasize the significance of this innovation. To this end, the studies of Hertz and Lipsett on the chemotherapy of choriocarcinoma will be reviewed, followed by some observations of our own experience using combination chemotherapy for a problem frequently encountered in clinical practice: advanced ovarian cancer.

Choriocarcinoma

Up to 1957, the experience with hysterectomy for trophoblastic disease of pregnancy left much to be desired: 41.4 per cent patients without metastases survived 5-years. Of those with metastatic disease, only 19.2 per cent lived five years.[2] In 1961 Hertz and Lipsett reported 47.5 per cent complete remissions in 63 patients with metastatic choriocarcinoma who received intensive Methotrexate (Figure I).[3] Subsequently, an additional 50 patients were treated with either Actinomycin D, Methotrexate or with both drugs given sequentially (Figure I). (Simultaneous administration is precluded by the overlapping toxicity of these two agents). About 50 per cent of the patients who were refractory to one of the two drugs were found to be responsive to subsequent administration of the other. By adding these to the remissions already induced by Actinomycin D alone (57 per cent) and Methotrexate alone (47 per cent), the overall remission rate for the entire group of 50 patients was increased to 74 per cent (Figure II). Significantly, at the time these results were first published, 29 of the 37 patients remitting had already remained free of evidence of active disease for longer than 24 months (by which time 98 per cent of patients treated with hysterectomy alone had expired).

FIGURE I
SCHEME OF SEQUENTIAL METHOTREXATE AND
ACTINOMYCIN D THERAPY

Methotrexate:	Actinomycin D
10-30 mg. I.M. daily for 5 consecutive days	7-12 γg/kg. I.V. daily for 5 consecutive days

Therapy continued in intermittent courses until 3 consecutive weekly 24 hour quantitative UCG determinations are normal.

As would be expected, the remission rate even with combination chemotherapy, declines with more advanced stages of trophoblastic disease. When disease had been present for more than four months before initiation of chemotherapy, remissions dropped from 79 per cent to 43 per cent; similarly only 37 per cent of patients with pre-treatment urinary chorionic gondotropin titers in excess of 1 x 10^3 units responded in contrast to 76 per cent remissions when titers were below this level.[3,4]

Carcinoma Of The Ovary

In advanced ovarian cancer, alkylating agents may induce objective regression in up to 60 per cent of the patients treated.[5] The duration of remissions, however, tends to be quite brief. In one study 12 per cent were sustained for more than six months and only 3 per cent beyond a year.[6] As a rule, chemotherapy is initiated in such patients at the time of relapse following initial radiotherapy.

Since prolonged hematopoietic depression can be demonstrated following pelvic radiotherapy,[7] long term chemotherapy adequate to maintain remission can only infrequently be tolerated with safety. It became evident, therefore, that for prolonged maintenance therapy a drug or drug combination with substantially less marrow toxicity must be devised.

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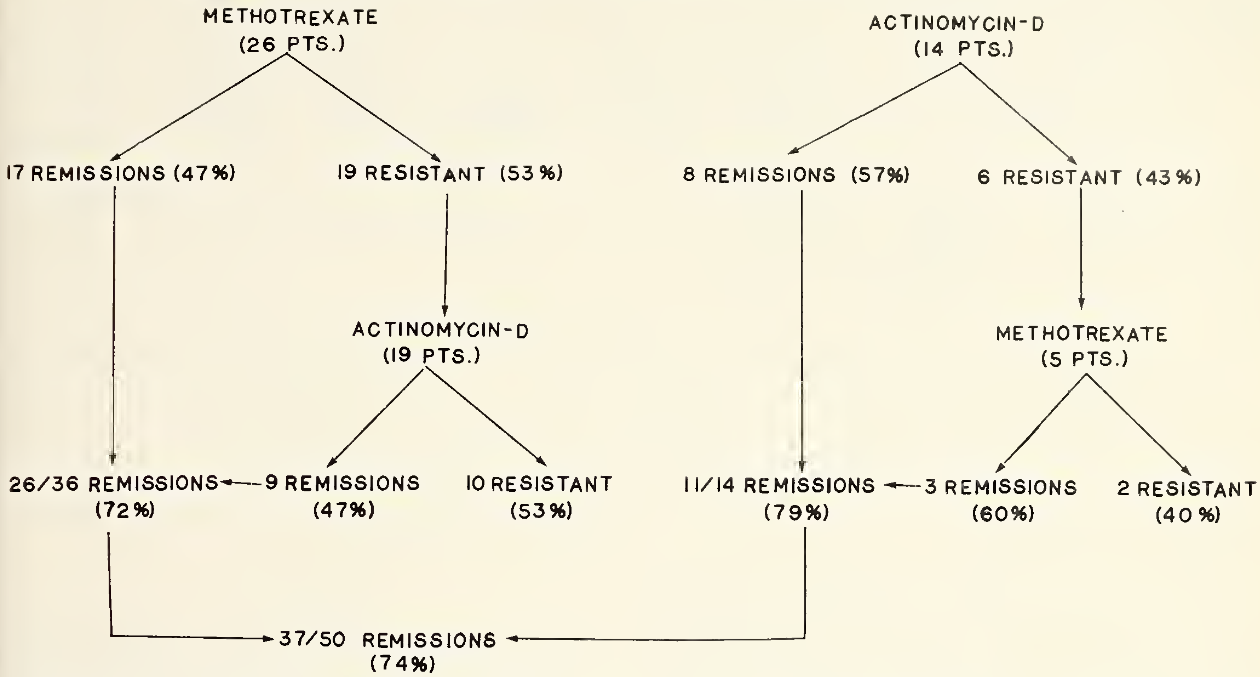
DR. HENRY M. WILLIAMS, Assistant Clinical Professor of Medicine.

FIGURE II

RESULTS OF METHOTREXATE-ACTINOMYCIN-D THERAPY OF CHORIOCARCINOMA (50 PATIENTS)*



* Ross *et al.* Am. J. Obs. & Gynec., 93: 223, 1965.

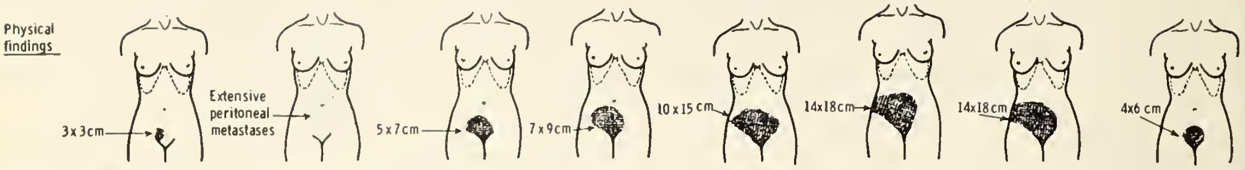
In 1964, having confirmed the observations of Durant and Lacher on the efficacy of low-dose combined Velban-chlorambucil therapy in Hodgkin's disease, we extended our study to problems in solid tumor therapy.[8] Initial observation of patients with metastatic breast or ovarian cancer demonstrated effective palliation without significant drug toxicity. Objective regression occurred in more than 60 per cent of the 30 ovarian carcinoma patients treated thus far with this drug combination. Sufficient time has elapsed to observe the full duration of remission in the majority.[9] With continuous maintenance therapy, remission could be sustained for more than 24 months (Figure IV). Even in those patients relapsing after intensive radiotherapy, serious toxicity was not incurred, and satisfactory regressions were observed (Figure V).

FIGURE III

VINBLASTINE-CHLORAMBUCIL STUDY DOSAGE SCHEDULE	URACIL MUSTARD-5-FLUOROURACIL DOSAGE SCHEDULE
INITIAL COURSE	
Vinblastine 0.1 mg/kg IV weekly	Uracil mustard 1 mg. P.O. daily
Chlorambucil 4 mg. P.O. daily	5-Fluorouracil 5 mg./kg. IV daily for 5 days
MODIFIED DOSE	
If WBC <3,000 reduce either or both: Vinblastine 0.05 mg./kg. IV weekly Chlorambucil 2 mg. P.O. daily.	If WBC <4,000 do not give 5-FU <3,000 also omit uracil mustard
MAINTENANCE THERAPY	
Vinblastine 0.1 mg./kg. IV every two weeks	5-FU 5 mg./kg. IV daily for 5 days repeated every 4 weeks
Chlorambucil 4 mg. P.O. daily	Uracil mustard 1 mg. P.O. daily

The clinical data, of course, do not bear on the issue of drug synergism. In mice bearing Sarcoma 180, significant increases in antitumor effect have been demonstrated when a combination of vinblastine and cyclophosphamide is used as compared to the results of treatment with either drug alone.[10] The increased effect (a 19 per cent prolongation of average survival time), was not of sufficient magnitude to suggest synergism. In the same system of mice, however, the combination of uracil mustard with 5-fluorouracil was synergistic, as evidenced by a 57 per cent increase in average survival time and a five-fold increase in the number of tumor regressions. Uracil mustard in this system was also potentiated by 6-thioguanine or 5-iodo-2-deoxyuridine. Curiously, although nitrogen mustard with 6-thioguanine produced an additive effect, the 6-thioguanine inhibition of Sarcoma 180 was not

PATIENT: M.J.: CARCINOMA OF OVARY



Date	1955	June 1961	Sept. 1963	Oct. 1963	Nov. 1963	Dec. 1963	Feb. 1964	May 1966
Symptoms	None: pelvic mass	Intestinal obstruction	Crampy abd. pain diarrhea	Unchanged	Less abd. cramps	Minimal abd. cramps	Same as in Dec.'63	No Sx except diarrhea
Treatment	Total hysterectomy + pelvic XR Rx (3000 r)	Ileo-transverse colostomy + XR Rx (3000 r to entire abd.)	Vinblastine q.2 weeks + chlorambucil daily	VLB + chlorambucil	VLB + chloramb.	VLB. + chloramb.	VLB. + chloramb.	VLB + chloramb.
HCT	-	30%	35%	32%	35%	31%	35%	31%
WBC	-	-	7,700	4,850	7,700	5,550	7,700	5,200

Figure IV

Velban-chlorambucil therapy of advanced ovarian cancer in relapse after two courses of intensive radiotherapy. Maximal regression was achieved in May, 1964, and, though not shown in above chart, is as illustrated for May, 1966. With continuous maintenance therapy, the patient remained clinically well throughout the two year period.

augmented by cyclophosphamide, chlorambucil, thioTEPA or Myleran.[11]

Because of this striking potentiation of uracil mustard by 5-fluorouracil, a clinical trial of low doses of uracil mustard combined with 5-fluorouracil was initiated in a series of patients with advanced ovarian cancer. Although sufficient time has not elapsed to permit accumulation of statistically valid data, some preliminary observations can be made.[12] There has been greater than 50 per cent objective regression in 14 of 18 patients who have received three or more courses of this combination. The duration of maintained remissions varies from four to fifteen months. Currently seven patients are still in remission up to 15 months after the onset of treatment. The initial results are sufficiently encouraging to warrant continued study of this combination under controlled conditions. Observation of patients throughout the full length of their remission should permit a more precise definition of the role of combination uracil mustard 5-fluorouracil therapy in the overall management of advanced ovarian cancer.

Summary

Combination chemotherapy of gynecologic cancer is reviewed briefly. The sequential use of Methotrexate and Actinomycin-D is currently the treatment of choice for human choriocarcinoma. Velban-chlorambucil, an empirical simultaneous drug combination, has facilitiated the management of advanced ovarian cancer, particularly of relapse following radiotherapy. In transmissible animal tumors, the effect of uracil mustard with 5-fluorouracil is synergistic. Preliminary studies in advanced ovarian carcinoma suggest that this combination may be of value in clinical cancer management.

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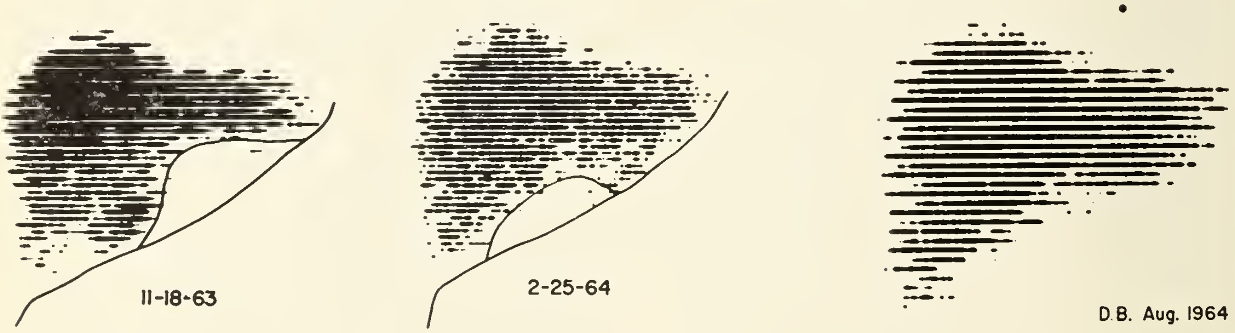

Figure V

Carcinoma of the ovary, initially treated with pelvic and upper abdominal radiotherapy. The large liver metastasis (11-18-63) heralded relapse. With Velban-chlorambucil therapy significant regression was achieved (2-25-64) and maintained satisfactorily until relapse in December, 1964.

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INCIDENCE vs PREVALENCE

The incidence of a disease is the number of new cases per number of persons in the population in a specific time period. The prevalence of a disease is the number of cases existing at any point in time in a given population. For example, in a study involving 5,000 people, if 250 are discovered to have rectal polyps in a two year period then the incidence of rectal polyps for this group is 25 per 1,000 per year. This is obtained by dividing 250 new cases for the two-year period by two in order to obtain the number of new cases per year and then dividing the result by five to get the number of new cases per year per 1,000 people.

Suppose now that at a given point in time—at the beginning of the experiment, at the end, or in the middle—count is taken of the number of *existing* cases of rectal polyps in this population. If 500 such cases are discovered the prevalence of rectal polyps would then be 10 per cent per thousand people. One must examine a person twice to determine incidence, only once for prevalence.

Think of it this way. About four million persons are born in the United States every year (incidence) but at a given point in time 185 million people are alive (prevalence) in the United States.—Stanley S. Shor, Ph.D., *Director*, AMA Department of Biostatistics.

Use Of Allopurinol For Control Of Hyperuricemia In Leukemia And Lymphoma

Ronald C. DeConti, M.D. and Paul Calabresi, M.D.

■ Hyperuricemia is a common finding in patients with leukemia and lymphoma. In the Memorial Hospital experience, 75 per cent of 203 patients with these disorders manifested hyperuricemia at some time during the course of their disease,[1] and 23 per cent reached serum levels above 12 mg/100 ml. A few patients develop prodagra, but the major consequence is impairment, either acute or chronic, of renal function. Overproduction of uric acid results in excretion of high concentrations of this poorly soluble end product of purine catabolism which may precipitate in the urinary tract, resulting in urate lithiasis and/or acute uric acid nephropathy. This latter complication has been cited as the chief cause of renal failure in these patients.[2] Rieselbach et al. have demonstrated marked reduction in inulin clearance in patients with hyperuricemia, even in the absence of overt renal failure.[3] Paradoxically, the dangers of precipitation of acute uric acid nephropathy have increased as our ability to palliate these conditions has improved. The large numbers of compounds capable of rapid cytotoxic effects on the neoplastic cell has made the development of uric acid nephropathy a well recognized complication of the treatment of these disorders.[4,5]

Traditional methods[6,7] of managing this complication have revolved around attempts to lyse cells slowly using small dosages of drug, improvements in hydration, alkylinization of the urine and osmotic diuresis; all are measures aimed at promoting the solubility of the uric acid presented to the kidney and each has at times failed. However, none of these measures influences the endogenous production of uric acid as a result of cell destruction and catabolism of purines. The development of allopurinol has radically altered our approach to this problem. This xanthine oxidase inhibitor effectively blocks the conversion of hypoxanthine to uric acid, thereby reducing the formation of uric acid and resulting in both lowered serum and urine uric acid levels. Inhibition of the formation of uric acid rather than the management of its excretion has become the central focus of this compound's use.

The data presented below were obtained as an extension of our earlier studies[8,9] specifically designed to investigate the effectiveness of this compound in reducing serum uric acid levels in patients with a wide variety of neoplastic disorders, particularly its value in preventing or controlling hyperuricemia in conjunction with vigorous oncolytic therapy.

Materials And Methods

CLINICAL MATERIAL

Thirty patients with leukemia or lymphoma who were treated with allopurinol at the Yale-New Haven Medical Center from July, 1965 to December, 1966, are included in this report. Hyperuricemia was present in ten of eleven patients with leukemia before institution of the proposed therapy. No serum uric acid determinations were performed prior to the initiation of therapy in Case 34.

Nineteen patients with malignant lymphoma received allopurinol, eight of whom manifested hyperuricemia before the onset of treatment. Allopurinol was begun within 24 hours of the initiation of the oncolytic therapy in all but Cases 42 and 63, which are described in Figures II and III. All patients were apparently well hydrated with good urine flow. Severe azotemia was absent in all. Patients received an ad lib diet without purine restriction.

DOSAGE OF DRUGS

Total daily doses of 200 to 800 mg. of allopurinol* were given by mouth in divided doses for periods of 1 to 4 weeks. Choice of antineoplastic therapy with alkylating agents, antimetabolites, steroids or irradiation was determined by the clinical situation and the agents were administered in the usual doses. (Tables I and II).[10]

LABORATORY STUDIES

Serum uric acid determination were done according to the method of Henry et al.[11] Blood samples were obtained between 8:00 and 10:00 a.m.

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* Kindly supplied as Zyloprim by Dr. George Hitchings, Burroughs Wellcome, Incorporated, Tuckahoe, New York.

From the Section of Oncology and Cancer Chemotherapy, Departments of Medicine and Pharmacology, Yale University School of Medicine. Supported by Grants (CA05944, T4 CA 5138-05,5MO1-FR-00038 and CA 8341-02).

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DR. PAUL CALABRESI, Associate Professor of Medicine and Pharmacology, Yale University School of Medicine.

Table I

Control of Hyperuricemia with Allopurinol in Patients with Leukemia during Antineoplastic Therapy

Case No.	Age Yr.	Sex	Diagnosis	Antineoplastic Therapy		Allopurinol Dosage mg/day	Serum Uric Acid	
				Agent	Effect		Before Allopurinol mg/100 ml.	After Allopurinol mg/100 ml.
34	1½	F	Acute lymphocytic leukemia	Prednisone 40 mg/day	WBC 135.0 → 14.0	200	—	3.5
35	6	F	Acute lymphocytic leukemia	Prednisone 40 mg/day 6-mercaptopurine 2.5 mg/kg day	Mass decreased	200	6.4	2.0
36	7	M	Acute lymphocytic leukemia	Cyclophosphamide 200 mg/day	WBC 8.0 → 0.8	400	7.2	1.5
37	14	F	Acute lymphocytic leukemia	Methotrexate 2 mg/kg by infusion Predisone 30 mg/day	WBC 92.0 → 3.3	400	10.3	4.5
38	49	F	Acute lymphocytic leukemia	Cyclophosphamide 30 mg/kg intravenously	WBC 104.0 → 40.0	800	8.8	5.6*
39	56	F	Acute lymphocytic leukemia	Cytosine arabinoside 1 mg/kg intravenously for 3 days	WBC 10.0 → 1.0	800	7.9	1.5
40	71	F	Acute lymphocytic leukemia	Cytosine arabinoside 1 mg/kg intravenously for 5 days	WBC 321.0 → 4.2	800	9.6	2.8
41	67	M	Acute myelomonocytic leukemia	6-mercaptopurine 150 mg/day Prednisone 40 mg/day	WBC 12.0 → 1.5	800	8.7	1.7
42	70	M	Acute monocytic leukemia	6-mercaptopurine 75 mg/day Prednisone 60 mg/day	WBC 175.0 → 1.5	600	9.9	2.5
43	46	M	Chronic granulocytic leukemia	Cytosine arabinoside 2 mg/kg intravenously for 5 days	WBC 450.0 → 2.5	600	8.5	3.2
44	55	M	Chronic granulocytic leukemia	Irradiation	Mass decreased	800	10.0	2.6

* 24 hours after Allopurinol.

with patients in the fasting state. When possible, several determinations were performed before allopurinol was initiated and thereafter, determinations were obtained every few days during the period of therapy. The hematocrit, hemoglobin, total and differential leukocyte counts, platelet count, hemoglobin, total and differential leukocyte counts, platelet count, urinalysis, blood urea nitrogen or serum creatinine, as well as liver function tests, were determined at regular intervals in most patients.

CLINICAL EVALUATION

In addition to the laboratory data described above, patients were observed for evidence of fever, dermatitis, podagra, urolithiasis or gastrointestinal dysfunction.

The antineoplastic effects of the oncolytic agents employed were assessed during the period of allopurinol administration. In patients with lymphoma, objective anti-tumor effects were classified as marked, moderate, slight or not significant, according to the extent of the response. A marked response was defined as greater than 75 per cent reduction in measurable tumor, a moderate response consisted of 50 to 75 per cent reduction in measurable disease and responses of 25 to 50 per cent were considered slight. Those of less than 25 per cent were classified as not significant. In patients with leukemia, cytotoxic effects were measured by comparing pre-treatment to post-treatment white blood cell counts or changes in the size of a particular mass. This evaluation referred only to the anti-

Table II

Effect of Allopurinol on Serum Uric Acid in Patients with Lymphoma during Therapy with Oncolytic Agents

CASE NO.	AGE YR.	SEX	DIAGNOSIS	ANTINEOPLASTIC THERAPY AGENT	ANTINEOPLASTIC THERAPY EFFECT	ALLOPURINOL DOSAGE MG/DAY	SERUM URIC ACID BEFORE ALLOPURINOL MR/100 ML.	SERUM URIC ACID AFTER ALLOPURINOL MG/100 ML.
45	65	F	Lymphocytic Lymphoma	Irradiation	Slight	800	3.0	0.6
46	53	F	Lymphocytic Lymphoma	Prednisone 60 mg/day	Moderate	600	5.2	1.8
47	49	F	Lymphocytic Lymphoma	Nitrogen Mustard 0.4 mg/kg intravenously	None	800	1.5	1.0
48	81	M	Lymphocytic Lymphoma	Chlorambucil	Slight	800	7.0	2.3
49	45	F	Lymphocytic Lymphoma	Nitrogen Mustard 0.4 mg/kg intravenously	Moderate	800	4.7	1.0
50	56	F	Lymphoblastic Lymphoma	Irradiation Prednisone 60 mg/day	Moderate	800	8.6	2.9
51	68	M	Lymphoblastic Lymphoma	Nitrogen Mustard 0.3 mg/kg intravenously	None	800	7.3	2.4
52	35	M	Lymphoblastic Lymphoma	Nitrogen Mustard 0.4 mg/kg intravenously	Marked	800	6.8	2.3
53	50	F	Lymphoblastic Lymphoma	Nitrogen Mustard 0.4 mg/kg intravenously	Moderate	800	7.9	4.0
54	56	M	Reticulum Cell Sarcoma	Vinblastine 0.1-0.4 mg/kg intravenously	None	800	7.9	2.6
55	55	M	Reticulum Cell Sarcoma	Irradiation	Moderate	800	9.6	2.7
56	65	M	Reticulum Cell Sarcoma	Irradiation	Moderate	800	5.6	2.2
57	46	F	Reticulum Cell Sarcoma	Nitrogen Mustard 0.4 mg/kg intravenously	Moderate	800	4.7	3.8
58	71	M	Reticulum Cell Sarcoma	Prednisone 60 mg/day	Slight	800	4.1	1.6
59	23	F	Hodgkin's Disease	Nitrogen Mustard 0.3 mg/kg intravenously	Marked	800	—	0.7
60	45	F	Hodgkin's Disease	Nitrogen Mustard 0.4 mg/kg intravenously	Slight	800	5.2	0.8
61	28	F	Hodgkin's Disease	Nitrogen Mustard 0.4 mg/kg intravenously	Marked	800	2.6	1.7
62	43	M	Hodgkin's Disease	Nitrogen Mustard 0.4 mg/kg intravenously	Moderate	800	5.8	2.7
63	67	M	Hodgkin's Disease	Prednisone 80 mg/day	Slight	800	19.0	3.6

neoplastic effects noted in the initial weeks of therapy and did not extend to possible late benefits.

Results

REDUCTION IN SERUM URIC ACID

Table I notes the representative serum uric acid levels achieved with allopurinol therapy in patients with leukemia. Despite uniformly elevated values prior to therapy, all values were reduced to within the normal range and many were distinctly low. In the children studied, 200-400 mg per day was as effective as the 600-800 mg per day dosage in adults. Serum uric acid values decreased within 48 hours and the greatest reduction occurred by the fifth day. These falls were achieved despite increased purine catabolism in all patients as judged by falls in leukemic leukocyte counts or diminished local masses.

The initial treatment with allopurinol in Case 42 was initiated only after effective methotrexate therapy had produced hyperuricemia (See Figure I). In this instance, allopurinol resulted in a sharp decline in the serm uric acid level and, subsequent treatment while on allopurinol did not reproduce hyperuricemia despite further evidence of leukemic cell lysis.

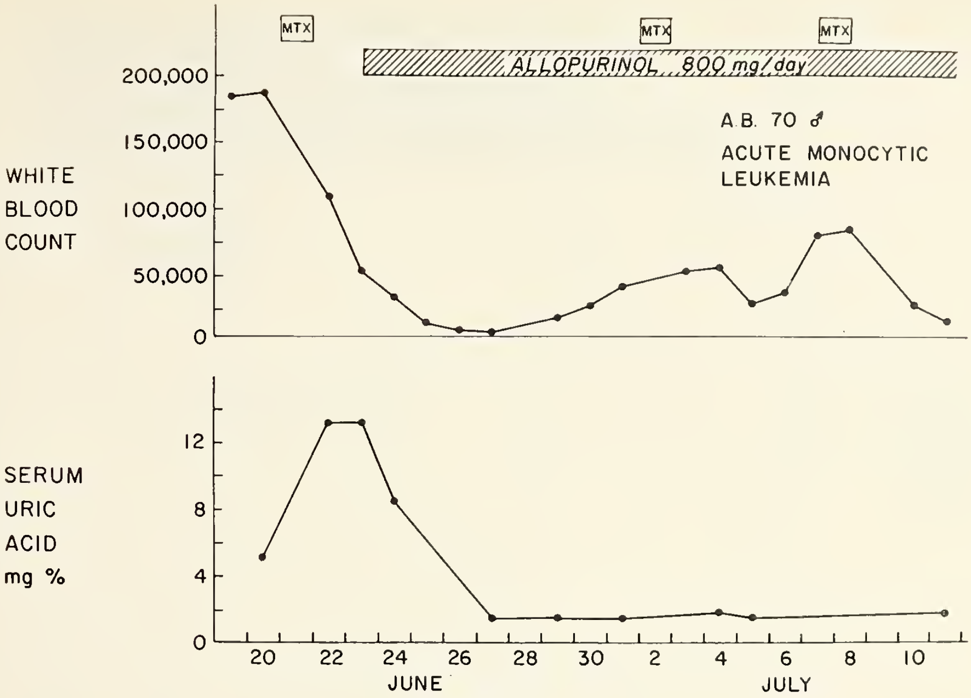

FIGURE I

In this patient (Case 42) rapid lysis of leukemic cells as a result of infusion therapy with methotrexate resulted in significant hyperuricemia. This was promptly reversed by allopurinol and low serum uric acid levels were maintained during subsequent treatment.

Table II depicts the effects of allopurinol on serum uric acid levels in patients with lymphoma. In this group, only 8 patients manifested hyperuricemia before therapy. Despite marked to moderate objective anti-tumor effects in eleven of the nineteen patients in this group, uric acid values were uniformly reduced in all patients to well below normal.

Two days prior to admission, Case 63 had been begun on prednisone therapy because of progressive cerebral symptoms and presented with a serum uric acid of 19 mg per cent. Institution of allopurinol therapy produced a sharp reduction in hyperuricemia and allowed continuation of prednisone therapy and initiation of cerebral irradiation. Subsequent systemic therapy with cyclophosamide did not produce an elevation of the serum uric acid.

TOXICITY

Allopurinol was well tolerated by most patients. Two of these thirty patients developed a widespread maculopapular eruption which persisted for approximately a week without other evidence of toxicity. Both these patients had received alkylating agents, anti-emetics or sedatives during this period of time and the cause of the drug eruption was not definitely established. Patients were not rechallenged with these agents. Podagra did not develop; renal function tests remained unchanged and liver function tests revealed no evidence of hepatic toxicity. Because of the antineoplastic agents employed, possible effects on the hematopoietic system could not be critically evaluated, though no unusual effects were observed.

Discussion

This study and its predecessor have clearly demonstrated the ability of allopurinol to both prevent and reduce the hyperuricemia associated with rapidly proliferating neoplastic tissues and suggest that the early use of this agent in situations where rapid effects of oncolytic therapy are to be expected may offer significant advantages as a means of preventing renal complications of therapy. Correction of hyperuricemia and hyperuricosuria is accomplished in a short period of time and is more effective than measures which further increase urate excretion. Oncolytic therapy has been demonstrated to increase urate excretion even without hyperuricemia.[12] The difficulties in predicting the rapidity of leukemic cell lysis, the rate of regression of lymphomatous masses, or the degree of hyperuricemia and hyperuricosuria which may develop, have encouraged the use of allopurinol in these disorders even in the absence of hyperuricemia. While some selected patients with sensitive carcinomas and already elevated serum uric acids may benefit from allopurinol therapy, the major application of this agent in neoplastic disease is its

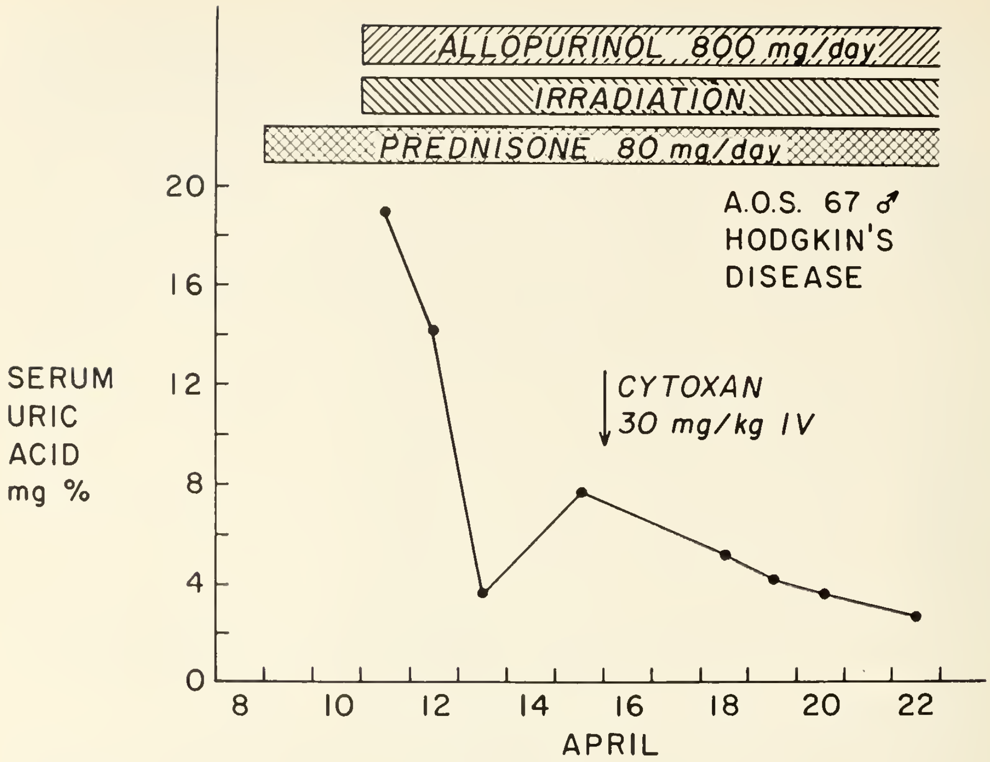

Figure II

Hyperuricemia in this man (Case 63) was induced by prednisone. The prompt return to normal values is typical of the effect of allopurinol. Allopurinol therapy permitted continuation of drug therapy, use of cerebral irradiation and treatment with cytoxan without elevations of serum uric acid levels.

use in myeloproliferative and lymphoproliferative disorders.

The safety and usefulness of allopurinol in the other major biochemical disorder characterized by hyperuricemia and hyperuricosuria, namely gout, have been demonstrated by many investigators.[13-15] In these studies, the dosages employed are often lower and the reductions in serum uric acid levels may be more gradual. However, the aim of treatment in this situation is to maintain normal serum uric acid levels for prolonged periods rather than acutely reducing serum uric acid levels during a short period of intensive antineoplastic therapy. Indeed, when applied to situations of chronic secondary hyperuricemia and hyperuricosuria, dosages of 400-600 mg. daily in adults are often sufficient to maintain a normal serum uric acid level.

Allopurinol was one of a number of pyrazalopyrimidine derivatives originally investigated as tumoricidal agents. Little anti-tumor activity was seen in compounds which did not produce hepatic toxicity. The application of the properties of the compound as a xanthine oxidase inhibitor were explored by Elion et al.,[16-18] in an attempt to potentiate the effects of 6-mercaptopurine by blocking its oxidation to 6-thiouric acid. These initial studies demonstrated the efficacy of the compound in reducing serum uric acid as well and fostered the development of this drug. Figure III shows the structural similarity between allopurinol and its analogs hypoxanthine and 6-mercaptopurine. By successfully competing with its natural substrate hypoxanthine and its synthetic analog 6-mercaptopurine, allopurinol binds the enzyme xanthine oxidase and in the reaction is converted to 4-6 dihydroxypyrazolo^{3,4d} pyrimidine, which also functions as an enzymatic inhibitor. This block is responsible for the failure of hypoxanthine and 6-mercaptopurine to be oxidized to their respective end products. As a result of this inhibition, the formation of biologically inert 6 thiouric acid from 6-mercaptopurine is prevented, reducing the effective dosage of 6-mercaptopurine by approximately 75 per cent. This effect on the metabolism of 6-MP should be carefully considered when the two agents are used together; otherwise serious hematopoietic supression may develop.

Allopurinol is well tolerated by the majority of patients. Perhaps its most striking complication is the possible precipitation of podagra in patients with gout. In our combined series of 63 patients, the only other complication noted was the develop-

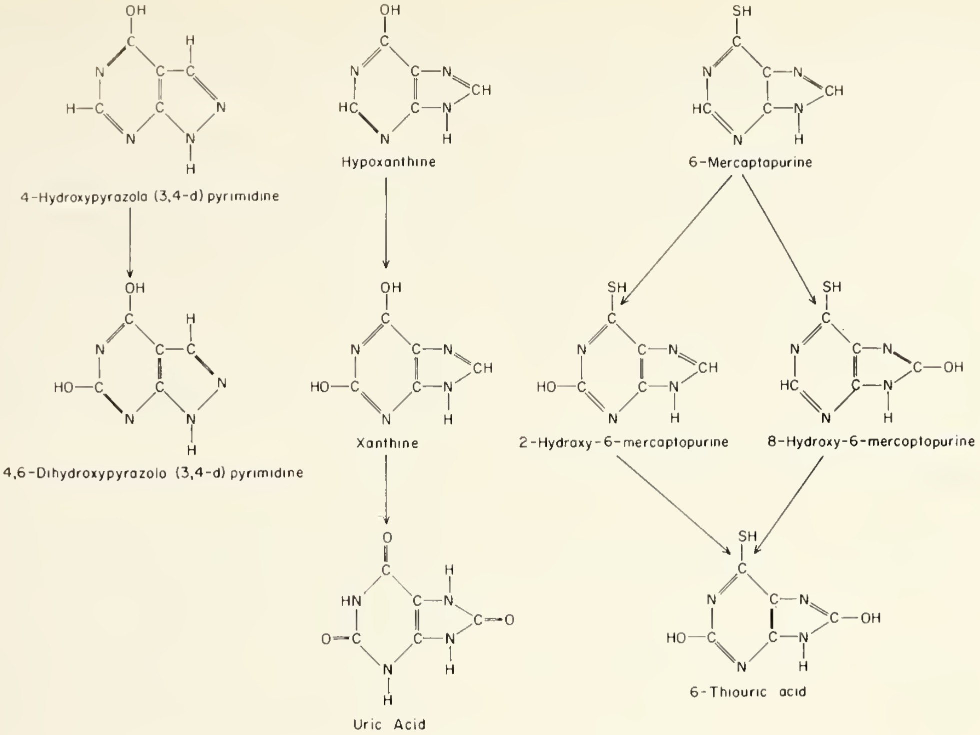
4-Hydroxypyrazolo (3,4-d) pyrimidine
4,6-Dihydroxypyrazolo (3,4-d) pyrimidine
Hypoxanthine
Xanthine
Uric Acid
6-Mercaptopurine
2-Hydroxy-6-mercaptopurine
8-Hydroxy-6-mercaptopurine
6-Thiouric acid

Figure III

The structural similarity and catabolic pathways of hypoxanthine and its analogs, 6-mercaptopurine and 4-hydroxypyrazolo (3,4-d) pyrimidine (allopurinol) are shown. All these reactions are catalyzed by the enzyme xanthine oxidase; by successfully competing for this enzyme allopurinol blocks the formation of uric acid and when 6-MP is present, prevents its oxidation to 6-thiouric acid. 4,6-dihdroxypyrazolo (3,4-d) pyrimidine also acts as a weak inhibitor of these reactions.

ment of a maculopapular skin eruption in 2 individuals. This has been estimated to occur in about 3 per cent of patients and in a few patients has been associated with fever, malaise and generalized aches.[19] To date, there has been no evidence that inhibition of xanthine oxidase leads to other metabolic complications. Inhibition of uric acid formation causes only a small elevation in serum oxypurines, because of their rapid renal clearance; further, the excretion of three end products of purine metabolism rather than one, each with an independent solubility product makes tissue deposits of xanthine or hypoxanthine unlikely. Renal calculi composed of xanthine have occurred in patients with hereditary xanthinuria, a disease characterized by an almost complete lack of xanthine oxidase,[20] but only at levels of urinary excretion of xanthine approximately six times those achieved with allopurinol.[21]

Summary

Allopurinol, a potent xanthine oxidase inhibitor, has been shown to be effective in reducing or preventing hyperuricemia in thirty patients with leukemia or lymphoma, when used in conjunction with antineoplastic therapy. It is suggested that early use of this agent in these disorders may prevent the renal complications (urolithiasis and acute uric acid nephropathy) which attend rapid effective oncolytic therapy.

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AN EARLY INVENTIVE AGAINST SMOKING 1638

"It drieth the brain, dimmeth the sight, vitiateth the smell, hurteth the stomach, destroyeth the concoction, disturbeth the humours and spirits, corrupteth the breath, induceth a trembling of the limbs, exsiccateth the windpipe, lungs and liver, annoyeth the milt, scorcheth the heart and causeth the blood to be adusted. In a word, it overthroweth the spirits, perverteth the understanding and confoundeth the senses with sudden astonishment and stupiditie of the whole body."—Dr. Veuner quoted from A. C. Corcoran: A mirror up to Medicine, Philadelphia, J. B. Lipincott Co., 1961, p. 298.

THE PRESIDENT'S PAGE

For the extremely popular and well attended scientific session at the 175th Annual Meeting of the Society sincere thanks must go to Dr. Rudolph Klare and his program committee. They arranged for outstanding speakers from far and near on a variety of new and recurring topics: from LSD and induction of ovulation to today's look at carcinoma of the breast. Likewise, the administrative office staff earned the admiration of all in handling so beautifully the logistics despite the augmented work load with the revised procedure in the House.

The Reference Committees were well attended and developed considerable constructive discussion. The members of the House cooperated throughout, and much business was transacted. In my remarks on taking office—published elsewhere in this issue since they were intended for the ears of the entire membership—the importance was pointed out of having physician representation on all committees and commissions involved in health care. Why in this era of specialization is the physician by-passed by the lay individual or organization in planning the protection and recovery of health for the public?

If we are to progress as effectively as possible, we must present a united front. The House only convenes twice a year, but innumerable committees work hard meanwhile and the Council sits once a month and a small group is working in the interest of the Society much of the time. It is impossible for every member to be fully informed and therefore be in a position to make each decision. Yet it is vital that each member take every opportunity to be aware of what is happening by perusing the condensed communications which are sent from time to time from the State office. The membership can scarcely imagine the time and effort expended by members of the legislative committee and others in the interest of all physicians of Connecticut and of their patients. Yet these people are not superhuman and when appeals are made for assistance, it is essential that help be forthcoming, such as by writing letters or talking to legislators, who incidentally are thirsty for factual resource material from you.

Hereafter, when the House of Delegates is in session, as many members of the Society as possible should attend reference committee meeting both to learn and to express their views. It is true that the decisions of the House may not always be in accordance with the thinking of all or even a majority of the members in a particular area. However, as is noted in the manual "Your Role as a Delegate to the CSMS House of Delegates," policy is established by vote of the House and "becomes the basic policy of the Society until such time as the 'loyal opposition' may be able to convince the majority of the membership of the House to reverse its official action." This same method prevails in the unions, and the laws of the country operate in similar manner. The officers of the Society are eager to cooperate with you. To be effective they need the active cooperation of the entire membership.

Unilateral or independent action by segments of the physician population may crystalize a small internal disagreement which appears as a major conflict in the eye of the public, or may work hardships on other physicians and promote internal rancor. Coordination and cooperation, on the other hand, are constructive.

How can I cooperate in politics or committees? I am not interested—nor qualified. Where is the magic? If you are interested in your patients, your relationship with them, your freedom to treat in the way you believe best, your right to develop a contract between you and the patient alone, and if you are intelligent and honest, then you are qualified—and vitally interested. Yes, these duties are time-consuming. It is easier to let your colleagues or your competitor do it. In this age of specialization, we have to be masters in our own field but must still be Jack of all trades. The temptation is to "let Joe do" those things which do not immediately concern the care of a particular patient. It is gratifying to see how many busy doctors, however, do participate in the active and long-term planning for the public's health care through their work on the various committees. Yet, some have complained that the organization is being run high-handedly and does not represent its members.

In unity is strength. We must strive to maintain our heritage of a high standard of practice and to overwhelm the insidious and blatant attacks which would result in its destruction, not by an immovable negativistic wall, but by constructive intelligent programs designed to meet the problems of the changing times. The Society needs your help. You need the Society's help. You are the Society.

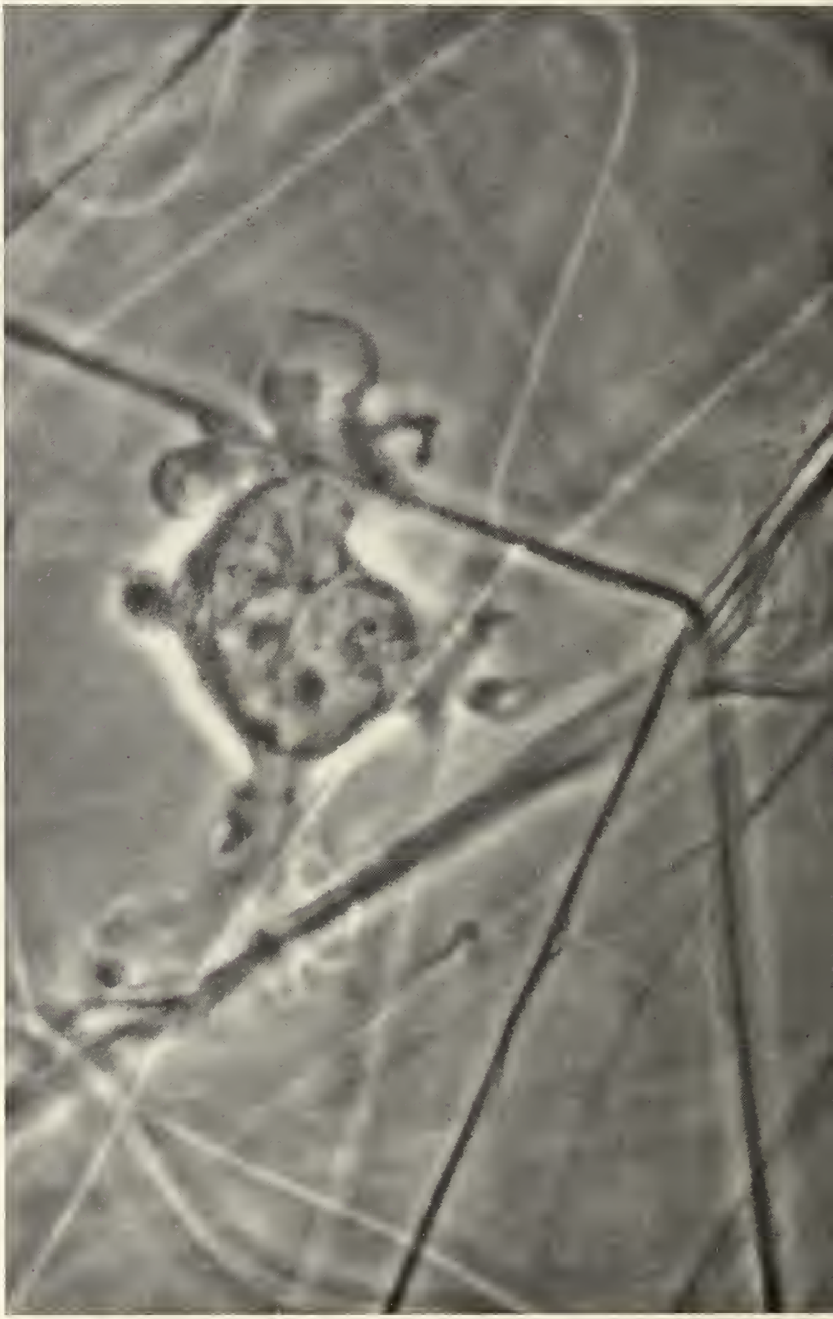
E. Tremain Bradley, m.d.

INFLAMMATION:
A cellular fight for life

A SYNTEX REPORT based on recently developed hypotheses about topical corticosteroids, including the cellular theories of inflammation by Thomas F. Dougherty, Ph.D., University of Utah.

You are looking at a fibroblast fighting for life. This cell—one of the most common found in connective tissue—has literally been poisoned by cytotoxins released from other cells that have ruptured. Soon, if the abnormal activity of this fibroblast does not cease, it, too, will rupture and die—one more casualty in the inflammatory wave of destruction precipitated by injury.

Until a short time ago no one had ever witnessed such a scene at the cellular level. Now, through advanced cinemicrographic techniques, it is possible to view and photograph the inflammatory process as produced experimentally in living animal tissue. This method permits new insight into the mechanism of inflammation and the role of corticosteroids in therapeutic management. Equally important, these techniques shed new light on factors that may make one corticosteroid more effective than another—factors that can be correlated with other chemical, biologic, and clinical parameters.



Worldwide clinical experience confirms the predictable therapeutic potential of Synalar

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Condition	Number of Publications	Number of Patients	Significant Improvement†
Contact Dermatitis	27	750	713
Eczematous Dermatitis	21	472	409
Seborrheic Dermatitis	18	442	426
Atopic Dermatitis	24	460	426
Psoriasis	36	1,699	1,510
Neurodermatitis	18	351	324
Total	144	4,174	3,808

*Complete bibliography on request.

†Expressed by the authors as excellent, very good, good, complete remission of inflammation, etc.

PRESCRIBING INFORMATION

For initiation of therapy: Cream 0.025%, 5 and 15 Gm. tubes, 425 Gm. jars; *for emollient effect:* Ointment 0.025%, 15 Gm. tubes; *for maintenance therapy:* Cream 0.01%, 15 and 45 Gm. tubes, 120 Gm. jars; *for intertriginous or hairy sites:* Solution 0.01%, 20 cc. and 60 cc. plastic squeeze bottles; *for infected inflammatory dermatoses:* Neo-Synalar® Cream (0.025% fluocinolone acetonide, neomycin sulfate, equivalent to 0.35% neomycin base), 5 and 15 Gm. tubes. CONTRAINDICATIONS: Tuberculous, fungal, and most viral lesions of the skin, (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. PRECAUTIONS: Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Prolonged use of any antibiotic may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy should be instituted. When severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. SIDE EFFECTS: Side effects are not ordinarily encountered with topically applied corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. The neomycin in Neo-Synalar Cream rarely produces allergic reactions.

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SUMMARY OF ACTIONS
COUNCIL MEETING
Thursday, April 20, 1967

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Hess. Bradley, Goldberg, Brandon, H. Caplan, Fabro, M. Caplan, Polivy, Rogol, Grendon, Egan, Abbot, Spitz, Hastings, Shepard, Nolan, Cramer, Petrie, Pelz, Wilson and Roch. Also present were: Mrs. Lindquist, Mr. Villano and Dr. Richards. Guests: Dr. Kernodle and Mr. Watson of AMPAC.

Absent were: Drs. W. Martin, Gardner, Ayres, Ciccarelli, Grant and Palomba.

II. Routine Business

Approval Of Minutes

As printed and distributed, it was VOTED to approve the minutes of the meeting of March 15, with the exception that note be made that the Committee on Maternal Morbidity and Mortality is asked to file a comprehensive "status" report on the program of admitting clean Gyn cases to maternity units *within one month*.

Life Memberships

It was VOTED to approve applications for Life Membership received from the following eligible Active Members:

Max Alpert, Bridgeport (FCMA)
James D. Corridon, East Norwalk (FCMA)
Isao Hirata, Sr., Woodbridge (NMCMA)
Anthony J. Loiacono, New London (NLCMA)
Sydney Mooney, Bridgeport (FCMA)
Robert Salinger, New Haven (NHCMA)
A. Lewis Shure, New Haven (NHCMA)

Recommendations Of The Fiscal Advisory Committee

It was VOTED to approve recommendations of the Fiscal Advisory Committee as follows:

(a) That the Society continue its membership in the New Haven Taxpayers Research Council and pay dues for 1967 in the amount of $30.00.

(b) That the Committee on Health Careers be authorized to spend up to $500 for an original and two copies of a film on Health Careers to be made from the video-tape of the Society's television presentation on that subject (WNHC-TV), and that the Chairman of the Committee be requested to contact the American Medical Association concerning AMA interest in purchasing copies of the film and/or helping to finance the costs of its production.

(c) That the Committees on Public Relations and Public Health be authorized to spend up to $200 to put on a conference on sex education for physician members of the Society (pursuant to a resolution adopted by the Council on February 16) to help them to become effective at local level in working with community programs on the problems of venereal disease, out-of-wedlock pregnancies, etc.; and that the Committees consider seeking pharmaceutical company subsidy and/or subscription by participants to cover the costs of luncheon (as planned by the Committees, at an estimated cost of $3.50 per person for approximately 130 participants).

Date Of Next Meeting

The organizational meeting of the newly-formed Council is to be called by the President "as soon as possible after the annual meeting of the House of Delegates."

III. Old, New And Special Business

Study Of Medical Staff Bylaws

It was VOTED to authorize the Committee on Preliminary Study of Censorship Questions to make a review and study of the medical staff bylaws in the community hospitals of the State, and to make a report and recommendations to the Council concerning same.

Educational Grant To COMPAC

It was VOTED to recommend to the House of Delegates on April 25 that authorization be given to the Treasurer to transmit to the Board of Directors of the Connecticut Medical Political Action Committee a check in the amount of $5,000 drawn from general funds, such monies to constitute a grant to COMPAC to be used for political educational activities only. There was considerable discussion concerning the desirability of maintaining continuing communication between the Council and the COMPAC Board, but no action was taken in this regard.

Reports—Committee On Third Party Payments

Three reports were received from the Committee on Third Party Payments, and these were acted upon as follows:

(a) *The NHCMA Resolution* (*H of D*, 12/65): It was VOTED to accept the report of the Committee on this subject as information, but to recommend to the House of Delegates the following procedures to deal with the "Report of the Council" on implementing the original NHCMA resolution, which was tabled for further study on 12/9/66:

(1) Remove the Report of the Council from the table

(2) Amend the Report by deleting the final paragraph in its entirety

(3) Accept the report as amended

It was further VOTED to present to the House of Delegates for adoption the so-called "substitute resolution," embodied in the deleted final paragraph of the Report just mentioned, as a matter for separate action. The resolution:

SUBJECT: PAYMENT FOR PHYSICIANS' SERVICES

WHEREAS: In the past, physicians have provided their own organized systems of private charity to indigent patients; and

WHEREAS: Governmental and other agencies have now assumed this prerogative; therefore be it.

RESOLVED: That the House of Delegates of the Connecticut State Medical Society adopt, as official policy, the opinion that the payment of usual and customary charges should be expected by physicians in private practice in return for their professional services, wherever and whenever rendered to any and all patients.

It was further VOTED to transmit to the House for consideration and action (but *without* recommendation) an amendment to the above resolution proposed by the Committee on Third Party Payments.

A suggested amendment:

RESOLVED: That physicians, individually or jointly, may voluntarily refrain from accepting any fee for their services for whatever reasons they may find appropriate.

(b) *Medicare B—Value of a Nursing Home Visit*: The Committee is of the opinion that Connecticut General should be guided by a policy that a physician's visit to a nursing home (extended-care facility) is equivalent in value to a house visit. It was VOTED to accept this opinion as information, and to request the Committee to elaborate further on the entire question (single visit vs. multiple visits; "emergency" visit vs. regular visit, etc.) and to seek further advice on the question from groups of practitioners concerned frequently with patient care in such facilities.

(c) *Continuing the CSMS Relative Value Study*: It was VOTED to receive as information the Committee's opinion that the Committee on Relative Value Study should continue as a permanent committee, having full representation from the various Sections and other groups, be given whatever clerical and statistical help that may be needed, and should review the RV Schedule periodically and make recommendations concerning changes in the unit values of procedures. *Further action in this matter by the Council will be necessary.*

Report—Advisory Committee To ODMC

It was VOTED to accept as information a report of this Committee on progress being made toward reaching a "usual and customary charge method" agreement with the Office of (Military) Dependents' Medical Care Program. In brief, the report indicated that apparently, at long last, ODMC is prepared to offer the Society a "usual and customary" charge agreement as soon as certain fee-level information applicable to various part of the State can be obtained from Connecticut General and/or other sources; also that a further extension of the several-times-extended 1965 agreement had been granted until July 31, 1967. The Committee expressed the opinion (informal) that if nothing concrete had been offered by ODMC as to the type of agreement desired before termination of the present extension, the Society might well wish to consider the desirability of continuing or discontinuing its relationship with the program. It was further VOTED to approve the extension recommended by the Committee.

Report—Liaison Committee On Paramedical Specialties

It was VOTED to receive as information a progress report of this Liaison Committee, filed with the Council by Hilliard Spitz, Chairman. In brief, the report indicates that the interest of the participants in defining mutual objectives is being sustained, and that monthly meetings will be continued. Some of the matters discussed have been: legislation before the 1967 General Assembly; proposed changes in nursing education—degree schools vs. hospital schools.

Resolution—Litchfield County Medical Association

It was VOTED to receive as information a resolution introduced for LCMA concerning recommended activities of the CSMS Committee on Rural Health with respect to the problem of supplying medical care in rural areas, but to defer action (adoption) on the resolution until it has been determined how many of the recommended activities for the Committee are already outlined in the bylaws. If substantially *not* covered in the bylaws, the resolution will be transmitted to the House of Delegates on April 25 for consideration.

CSMS—County Annual Meetings

Note was made that the provisions of the Charter with respect to the holding of annual meetings of the Society in relation to annual meetings of the component county associations have not been properly observed in recent years; i.e., the county meetings are being held much later than the required "at least twenty days before" the state meeting. It was VOTED to bring this matter to the attention of the component associations and ask for their cooperative compliance with the Charter. However, to obviate the need for the county organizations to change their bylaws, it is planned to hold future meetings of the Society on or about May 15 (including 1968, if possible) on the basis that all county meetings will have been held before the beginning of the last week in April.

Replacement—Board Of Examiners For Hypertrichologists

Having been notified that Reginald E. Gillson, Branford, has resigned as a member of the State Board of Examiners for Hypertrichologists, it was VOTED to recommend Jack J. Albom, New Haven, to the Governor for appointment to replace Dr. Gillson on the Board for the balance of the unexpired term, July 1, 1966-June 30, 1969.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on April 20, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT OPPORTUNITIES

OBS-GYN—Board certified Obs-Gyn needed to associate with another Obs-Gyn in a large industrial city in Southern Connecticut, leading to eventual partnership. Hospital staff privileges available at two community hospitals.

PEDIATRICIAN—Pediatrician to associate with two established pediatricians in Southern Connecticut coastal town. Liberal salary first year, then partnership.

PHYSICIAN with background in internal medicine and/or pediatrics who is interested in a group practice in a rural town in Southern Connecticut. Hospital services available at several area hospitals.

G.P.—For association with another physician in a well-established practice in a growing industrial city in Southern Connecticut. Partnership possible after one year.

DIRECTOR OF PSYCHIATRIC TRAINING —Board certified. To direct 3-year approved psychiatric residency program at a 2000 bed, community oriented, decentralized mental hospital. Also, to coordinate education for nurses, psychologists, social workers and occupational therapists in approved and university affiliated programs. Previous teaching experience necessary. Starting salary range: $17,660-$19,850, excellent fringe benefits. All particulars should be sent in first letter, including references. Write: Superintendent, Connecticut Valley Hospital, P. O. Box 351, Middletown, Connecticut 06458.

PSYCHIATRIST needed for a community oriented mental hospital. To direct work in a 300 bed comprehensive mental health center, one of several units in a 2100 bed state mental hospital. Opportunity for teaching, clinical work and research. To work with a team of social workers, psychiatric residents, psychologists, occupational therapists and nursing staff. OPD, day-care, in-patient consultation and emergency care available. Opportunity for association with Wesleyan University, Yale University and UConn. Starting salary: $14,240 to $18,220, annual pay increases. Excellent fringe benefits. All particulars and references in first letter. Write: Mehadin K. Arafeh, Superintendent, Connecticut Valley Hospital, Box 351, Middletown, Connecticut 06458.

G.P. to specialize in psychiatry. Psychiatric residencies available in community oriented mental hospital. Associate with Yale University Departments of Psychiatry and Neurology, which provides clinical demonstrations, teaching and supervision in hospital. Opportunities for training in areas of special interest. Special arrangements can be made for residents to be accepted for degrees in community mental health and hospital administration at Yale School of Epidemiology and Public Health. Psychoanalytic training available at Western New England Psychoanalytic Institute. Salary: $12,000 annually under NIMH grant. Excellent fringe benefits. All particulars and references should be sent in first letter. Write: Superintendent, Connecticut Valley Hospital, P. O. Box 351, Middletown, Connecticut 06458.

STAFF PHYSICIAN for Masonic Hospital in Wallingford, Connecticut. Pay above average, with interesting work.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

Mild mood depression, poor appetite, little interest in the present or future. Does this picture mean that she's giving in to functional fatigue?

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Each 45 cc. (3 tablespoonfuls) contains: alcohol, 15%, pipradrol hydrochloride, 2 mg.; thiamine hydrochloride (vitamin B_1) (10 MDR*), 10 mg.; riboflavin (vitamin B_2) (4 MDR), 5 mg.; pyridoxine hydrochloride (vitamin B_6), 1 mg.; niacinamide (5 MDR), 50 mg.; choline,† 100 mg.; inositol,† 100 mg.; calcium glycerophosphate, 100 mg. (supplies 2% MDR for calcium and for phosphorus) and 1 mg. each of the following: cobalt (as chloride), manganese (as sulfate), magnesium (as acetate), zinc (as acetate), and molybdenum (as ammonium molybdate).

*Multiple of adult Minimum Daily Requirement supplied.
†The need for these substances in human nutrition has not been established.

Indications: 1. Functional fatigue such as that often associated with: a depressing experience or stressful time of life; advancing years; convalescence; limited activity or confinement. 2. Poor appetite and vitamin-mineral deficiency as they occur in: patients having faulty eating habits; geriatric patients who are losing interest in food; patients convalescing from debilitating illness or surgery.

Contraindications: As with other drugs with CNS stimulating action, Alertonic is contraindicated in hyperactive, agitated or severely anxious patients and in chorea or obsessive compulsive states.

Side effects: Reports of overstimulation have been rare. Patients who are known to be unduly sensitive to the effects of stimulant drugs should be observed carefully in the initial stages of treatment.

Dosage: Adults, 1 tablespoonful; children (over 15 years old), 1 to 2 teaspoonfuls; children (4 to 15 years old), 1 teaspoonful. To be taken three times daily 30 minutes before meals.

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SUMMARY OF PROCEEDINGS
HOUSE OF DELEGATES — ANNUAL MEETING
Hartford, Connecticut — April 26, 1967

REPORTS AND ADDRESSES

The House received a number of reports and/or addresses from the officers of the Society. Several of the reports submitted in printed form will appear at the end of this summary.

Election Of Officers, Committees, Advisors And Representatives

The officers elected at this meeting of the House were:

President: E. Tremain Bradley, Norwalk
President-Elect: Norman H. Gardner, East Hampton
Vice-President: Stevens J. Martin, Hartford
Secretary: Charles Polivy, Hartford
Treasurer: David A. Grendon, Sharon
Speaker of the House: Kenneth F. Brandon, Hartford
Vice-Speaker of the House: Henry Caplan, Yalesville
AMA Delegates (January 1, 1968 to December 31, 1969): Norman H. Gardner, East Hampton; Michael A. Dean, Bridgeport (Alternate)
Councilor-at-Large: Orvan W. Hess, New Haven

A full slate of Boards, Committees, Advisors, Representatives, etc. was also elected by the House. Each member of these groups will be formally notified of his or her election by letter and the membership of all Boards, Committees, etc. will be published in the August 1968 Roster.

Delegates From Other Medical Organizations

Introduced to the House and making brief remarks were:

John P. Dow: Delegate from the Maine Medical Association
Theordore H. Lee: Delegate from the New Hampshire Medical Society
John C. Twitchell: Delegate from the Vermont State Medical Society
Robert W. Buck: Delegate from the Massachusetts Medical Society
Henry I. Fineberg: Delegate from the Medical Society of State of New York
Lloyd A. Hamilton: Delegate from the Medical Society of New Jersey

Presentation And Awards

1967 CSMS Press Awards

E. Tremain Bradley, President, presented the following winners of the Connecticut Medical Press awards with a check in the amount of $150.00 and a bronze engraved plaque:

David Rhinelander, Hartford Courant—Feature Writing
Ivan Robinson, Hartford Times — News Reporting
Editorial Team: John Cleary, William Dougherty, Sereno Gammel—Editorial Writing

AMA-ERF Grants For 1967

Presented by retiring President Orvan W. Hess, AMA-ERF checks were received by the Yale University School of Medicine and the University of Connecticut Medical School.

Accepting these grants were:

Arthur Ebbert, Jr., Associate Dean, Yale University School of Medicine, ($5,365.88)
William Fleeson, Associate Dean, University of Connecticut Medical School, ($2,864.38)

Presentation Of Past President's Pin

In appreciation of his many contributions to the Society and its members, Orvan W. Hess, New Haven, received a Past President's Pin as he retired from office (1966-67). Making the presentation was Stevens J. Martin, Hartford, Chairman of the Council.

Major Actions Taken

At this session, the Reference Committee approach to transacting all of the business of the House of Delegates was used for the first time in recent years. The hearings of the Committees (four of them) were open to all members of the Society, whether or not they were delegates. Acting on the reports of the Reference Committees, the House of Delegates took major actions as follows:

Educational Grant To COMPAC

It was VOTED to authorize the Treasurer to draw a check in the amount of $7,500 on the Society's general fund, and to transmit same to the Board of Directors of the Connecticut Medical Political Action Committee to be used for political educational activities only.

Resolution: Surgical Cases On Obstetrical Floors

The following resolution on this subject was adopted and referred to the Council for implementation:

WHEREAS: The admission of clean gynecological cases to the obstetrical floors of hospitals is no longer a "pilot study" program; and

WHEREAS: Other physicians and surgeons admit such clean cases to other floors of hospitals, therefore be it

RESOLVED: That the House of Delegates of the Connecticut State Medical Society express the opinion that all physicians with admitting privileges granted by a given hospital for the care and treatment of "clean" cases on other floors also be allowed to utilize the available beds on obstetrical floors, in accordance with the rules and regulations of the Department of Obstetrics and Gynecology of the hospital concerned, if it is approved for this program.

Resolutions: Payment For Physicians' Services Under Title XIX

Two related resolutions dealing with this subject were adopted (and have been implemented) as follows:

SUBJECT: OPPOSITION TO FEE SCHEDULE FOR TITLE XIX

RESOLVED: That the House of Delegates of the Connecticut State Medical Society again go on record as opposing any fee schedule, no matter how worded, being used in the implementation of Title XIX; and be it further

RESOLVED: That the Commissioner of Welfare and, with adequate explanation, the Legislature of the State of Connecticut, be so apprised; and be it further

RESOLVED: That the Committee on Third Party Payments, the Advisory Committee to the State Commissioners of Welfare, Finance and Control, and the Committee on State Legislation of the Connecticut State Medical Society be apprised of this action in the hope that the position of the Connecticut State Medical Society will be made clear to all concerned before any adverse legislation is passed and in the hope that the Commissioner of Welfare, in his implementation of Title XIX, will use the non-schedule, usual and customary charge method of payment for physicians' services.

SUBJECT: THE USUAL AND CUSTOMARY CHARGE METHOD OF PAYMENT UNDER TITLE XIX

RESOLVED: That the House of Delegates of the Connecticut State Medical Society reaffirm the policy that, as clearly defined in its previous actions, usual and customary charges should be the basis for payment of physicians for services rendered to all beneficiaries of Medical Assistance under Title XIX; and be it further

RESOLVED: That all committees and representatives of the Society charged with seeking to gain acceptance of the usual and customary charge method of payment by the 1967 General Assembly in its implementation of a Title XIX program of Medical Assistance be immediately apprised of this reaffirmation; and be it further

RESOLVED: That all such committees and members also be apprised of the opposition of the House of Delegates to a fee schedule of any type in the implementation of Title XIX; and be it further

RESOLVED: That all members of the Society be urged to contact promptly their state representatives and senators seeking their support of the usual and customary charge method of payment, as authorized by the Secretary of HEW, in the implementation of Title XIX in Connecticut.

Resolution: Payment For Physicians' Services

A general resolution related to the foregoing specific resolutions on Title XIX was also adopted, as follows:

SUBJECT: PAYMENT FOR PHYSICIANS' SERVICES

WHEREAS: In the past, physicians have provided their own organized systems of private charity to indigent patients; and

WHEREAS: Governmental and other agencies have now assumed this prerogative; therefore be it.

RESOLVED: That the House of Delegates of the Connecticut State Medical Society adopt, as official policy, the opinion that the payment of usual and customary charges should be expected by physicians in private practice in return for their professional services, wherever and whenever rendered to any and all patients.

Resolution: Open Policy In Hospital Staff Appointments

It was voted to transmit to the June meeting of the AMA House of Delegates a resolution on this subject, to read as follows:

WHEREAS: All aspects of rendering patient care by physicians constitute the practice of medicine; and

WHEREAS: To assure maximum freedom of choice of physician by the patient, and of consultant by his attending doctor, has been, and is, a fundamental goal of practitioners of medicine; and

WHEREAS: A double standard of policy often exists between so-called "hospital-based specialists" and other types of practitioners with respect to hospital staff appointments, a "closed" policy frequently applying to the former while an "open" policy usually applies to the latter; and

WHEREAS: Under a variety of financial arrangements, there is an increasing trend in many parts of the country to classify nearly all types of practitioners as "hospital-based" for the purpose of enabling institutions to provide medical services as well as hospital services; and

Whereas: This increasing trend, coupled with a "closed" policy with respect to staff appointments for physicians having such financial arrangements with hospitals, can lead to increasing limitation of free choice of physicians by patients and free choice of consultants by other staff members; therefore be it

Resolved: That the House of Delegates of the American Medical Association endorse the principle of completely "open" policy with respect to staff appointments among all physicians having equivalent credentials in all hospital departments and services as a means of assuring maximum freedom of choice of physicians by patients, and of consultants by staff members, among all available, and qualified doctors of medicine practicing in the hospital's community area; and be it further

Resolved: That the House of Delegates urge the constituent state, and component county, units of the American Medical Association to bring this endorsement to the attention of the medical staffs of all hospitals operating within their jurisdictions, and to urge such staffs to carefully consider the merits of adopting such "open" policy with respect to all staff appointments in all hospital departments and services.

Resolution: Compulsory Generic Drug Prescribing

It was voted to adopt a resolution on this subject, as follows:

Resolved: That the House of Delegates of the Connecticut State Medical Society express continued opposition to compulsory generic prescribing of drugs by physicians, regardless of the status of the patient; and be it further

Resolved: That all U. S. Representatives and Senators from Connecticut be apprised of this action; and be urged to oppose the enactment of any legislation calling for such compulsory generic prescribing by whatever means.

Resolution: Opposition To S-110, 90th Congress

It was voted to adopt a resolution on this subject as follows:

Whereas: Senator Aiken (R-Vermont) and others have proposed S-110 which amends Title XVIII of P.L. 89-97 in a manner inimical to medical freedom of physicians; and

Whereas: The Section entitled "Specialists Professional Services" would return the hospital specialists to total control by the hospitals by removing reimbursement for their services from Part B and placing it in Part A and thus set a pattern for future control of all physicians; and

Whereas: The Section entitled "Schedule of Maximum Fees Governing Payment for Physicians" states:

> "The amount of such fees shall be so established as to coincide, to the maximum extent possible, with the fees allowed in the locality by carriers for policyholders and subscribers under other health insurance programs"; and

Whereas: The Section entitled "Coverage of Expenses of Certain Drugs" would set up a national formulary giving preference to the cheapest of supposed generic equivalents; and

Whereas: These provisions of S-110 corroborate the previous contentions of many that the ultimate result of such legislation will be total control of all phases of medical care; therefore be it.

Resolved: That the House of Delegates of the Connecticut State Medical Society oppose these sections of S-110; and be it further

Resolved: That all U. S. Representatives and Senators from Connecticut be apprised of this action and be urged to oppose enactment of these sections of S-110.

Definition Of Term "Medically Necessary"

Recognizing that the component county associations may be called upon with increasing frequency by third party payors to give opinions regarding the medical necessity of medical services rendered by physician members, it was voted to approve a definition of the term "medically necessary" as follows:

For the Physician: Any professionally recognized medical service that is prescribed and/or rendered by a licensed physician, which is in reasonable accord with the customary standards of medical practice obtaining in his community area, should ordinarily be accepted without question as being "medically necessary" by the patient and/or a third party payor. When the medical necessity of such a service is questioned by the patient and/or a third party payor, the question should be referred promptly for review and opinion to the county medical association of which the physician is a member.

For the Patient: Any professionally recognized medical service that is prescribed and/or rendered in good faith by a licensed physician to a patient consulting him should ordinarily be accepted without question as being "medically necessary" by third party payors. When the medical necessity of the patient's request for consultation with the physician is questioned by a third party, such question should be resolved exclusively by the patient and the third party payor concerned.

Council Report On Implementation Of NHCMA Resolution (House Of Delegates 12/5/65)

On December 5, 1965, the House of Delegates adopted a resolution introduced by the New Haven County Medical Association which directed the Council to take steps to attain the "institution of payment for heretofore unpaid services of physicians" and to report to the House of Delegates the Council's "accomplishments" in implementing this and related purposes. The substance of the resolution was:

Be It Resolved: That the House of Delegates of CSMS direct the Council to undertake the accomplishment of the following objectives:

(1) Institution of payment for heretofore unpaid services of physicians to local and state in-hospital and out-patient welfare recipients.

(2) Provision for fee-for-service attendance at privately operated clinics and other medical care facilities.

and be it further

Resolved: That in all negotiations in these matters, the Council utilize the formulas provided by the Relative Value Schedule adopted by the CSMS House of Delegates in April, 1965.

The Council promptly referred the resolution to the Committee on Third Party Payments for study and report. Meanwhile, however, that Committee was actively engaged in developing policies regarding third party payments for physicians services—with special emphasis on governmental agencies as the payors, and these policies were subsequently adopted by the House of Delegates at the 1966 Annual Meeting last April. In brief, these policies declared that physicians should be paid on the basis of "usual and customary fees, as determined at local level"; that the Relative Value Schedule should be used as a guide; and that the county associations should undertake a review of any usual and customary charges which were questioned.

Our Advisory Committee to the State Commissioners of Welfare, Finance and Control has sought implementation of these policies by the Welfare Department in the new Title XIX program of Medical Assistance which went into effect on July 1 of this year, but the final details of which (standards of eligibility, appropriation of funds, etc.) must await action by the 1967 General Assembly. Commissioner Shapiro has pledged his support to our policies, in principle, and it is expected that we will be able to file a report with the House at the December 8 meeting on whether they will be adequately funded in the budget which he has submitted to the legislature for the next biennium.

Similarly, our Advisory Committee to the Military Dependents' Medical Care Program (formerly called "Medicare") has entered into negotiations with that branch of the Federal government to embody the same policies in that program; i.e., the concept of usual and customary fees, as determined at local level. While these negotiations are continuing, the Council has authorized extension of the old 1965 Agreement with ODMC but has declined to sign any new agreement or any new amendments to the basic agreement until a plan reasonably embodying our policies has been developed and subjected to careful study by our several committees, and, ultimately, by the House.

Finally, our Committee on Medical Care of Veterans has been directed to advance the same policies with the VA's officialdom, and we expect to have a report on the progress being made by that Committee in the near future.

In summary, then, the Council feels that through these efforts much has been accomplished toward implementing the over-all purposes of the New Haven Association's resolution. If completely successful, their effects will ultimately be felt even in privately operated clinics and other medical care facilities. In the latter areas, however, it is the feeling of the Council that each physician or group of physicians must assume responsibility for making financial arrangements, including reimbursement through third party mechanisms, which are satisfactory not only to themselves but also are approved by the medical staffs of such clinics and facilities.

ADDRESS OF THE PRESIDENT

It is indeed a privilege and a pleasure for me to address you on the occasion of this 175th Annual Meeting of the Connecticut State Medical Society The past year has been a stimulating and pleasant experience and a particular honor for me as your President.

Among the numerous duties and opportunities that have been mine, one of the most gratifying has been the privilege of getting to know so many more of my colleagues in medicine throughout the State. I regret that, due to overlapping engagements, it has not been possible for me to be present at all of the County Association Meetings.

In many ways, the past year has been historic. It has been a year of not only changing concepts and relationships in the national social order, but also one of enforced transition in some aspects of Medicine. In the process of adapting to these modifications, there have been some difficulties and inevitable differences of opinion.

Your leadership has encouraged a free expression of varied points of view. It is on this principle that decisions are reached by the Council in its attempt to act in the best interest of all concerned.

Your Council, Officers, and Executive Staff have been most dedicated in carrying out their ever-increasing responsibilities.

The Chairmen and Members of the numerous Committees have given much time and effort on our behalf throughout the year, and I, as President, am most grateful and appreciative to each and every one of them for doing a fine job. While acting on their important reports which you have before you today, I am sure you will all recognize the considerable time and labor they have given voluntarily to carrying out these assignments.

Doctors Klare, Babbott and Eckhardt, have planned an outstanding scientific program for this meeting. Discussions of numerous subjects of current interest will also be conducted under the auspices of the Society.

I urge you to view the exhibit featuring works of art by our physicians and their families and to visit the booths provided by our colleagues in the pharmaceutical and other industries whose generous support helps to make our meetings possible. I believe you will find the exchange of information and the renewal of old friendships pleasurable and worthwhile.

You have received reports by our Officers, Council and Committees on activities throughout the year. Further details are contained in your Delegate's Handbook. This will provide information for your deliberation in developing policies and programs of action for the coming months. A manual on your role as a Delegate has been sent to you. I hope you have studied it and will refer to it often during the House of Delegates meeting.

At this time, I wish to give credit to Dr. Bradley, and his committee, for the introduction in this session of the House of Delegates an extended use of Reference Committees. I trust this innovation, which appears to have considerable merit, will serve to expedite the business before you.

Many of the objectives sought during the year have been achieved. Others must be carried on by the incoming President and your elected representatives. The Society has continually maintained a spirit of cooperation and has given constructive support to many activities of civic and professional groups that are vital to medicine and the community. Several facets of the Society's interrelationship with hospitals, agencies, medical schools and other organizations have been reinforced. New ideas and projects in progress will require much time, concentration and effort by all our members during the year ahead.

In reviewing my year in office, a few activities and accomplishments which represent high-water marks in our efforts to create a more effective medical society might be mentioned:

1. The inauguration of County Officers Conferences which bring together county and state officers for face-to-face discussions of common problems. These conferences have met with success. I am confident they will continue to be held in the future.

2. The activation of the President's Ad Hoc Committee on Reorganization and Planning which made a comprehensive study of the Society's structure and operating procedures. Changes which were badly needed were recommended to the Council.

3. In advance of and in preparation for the implementation of the Medicare Program on July 1, 1966, as your President, I attended a White House Conference on national medical leaders. I also attended a Special Session of the AMA House of Delegates at which resolutions on direct billing and individual responsibility of participation were adopted.

4. Launching of the Medicare Program in Connecticut without protest or problems on the part of physicians. I am pleased that our members have adapted their practices so well to the demands of the law and I am proud of their attitude of responsibility to their patients and to society as a whole.

5. Attendance by your President at a national conference on Regional Medical Programs to learn about and understand its implications before it was established in Connecticut. This program, authorized by the DeBakey legislation, promises to be as revolutionary as Titles XVIII and XIX programs.

6. Participation in the celebration of the 200th Anniversary of the founding of Litchfield County Medical Association to confer honorary degrees and awards on behalf of the Connecticut State Medical Society. One recipient has subsequently been awarded a Nobel Prize for his contributions to cancer research.

7. Advancement and expansion of our legislative interests in the State Capitol by meeting directly—and I hope effectively—with leaders and other members of the General Assembly, not only at public hearings but also for the first time, in corridor meetings, in executive session, in special conferences, etc.

In addition to bearing the burden of daily responsibilities of administering medical care for our patients, fulfilling the demands of special pursuits for the advancement of science, and giving time to teaching of medicine, it has been necessary for us to concern ourselves with the new economic plans to provide medical services for the citizens of Connecticut. Thus far, these plans have placed emphasis primarily on making services available for those persons whom society deems to be in need of financial assistance for their health care. The over-riding concern of the Profession has been that these programs assure the Public a continuation of the provision of high quality medical care. In fact, current legislation indicates the objective of removing the stigma of "Welfare Medicine."

The implementation of Title XVIII of the Medicare law has been complicated in interpretation and has added problems in the administration of this technique of remuneration for services for those over 65. Difficulties have been encountered with overcrowding and serious delay in admission of patients to some of our hospitals. More disappointment may be anticipated as future demands on extended care facilities and manpower occur. To date, there has been little intereference with the usual methods by which medical services are provided. Nevertheless, almost constant supervision of proposed new legislation or amendments to existing Medicare laws is required. It is important that these bills be scrutinized carefully and support given to those measures which are clearly in the interest of the patient.

Up to the present, experience with the fiscal intermediary in this State has been reasonable satisfactory, as all parties adjust to the numerous requirements of the regulations. This has been, in part, due to the active and cooperative liaison between representatives of the State Society and Connecticut General with its accomulated experience in the field of medical insurance.

More recently Title XIX, "Medicaid," with its impending implications for Connecticut, has received very close attention of the Society. This legislation, which is based on the principle of providing financial assistance for the medically needy on a Federal-State matching arrangement, has met the approval of the Profession. Eligibility for service is limited, at present, to specific categories and income levels. It is expected that by 1975, all "medically needy" will be included under this plan for financial assistance. As you are aware, your State Society has submitted bills to the legislature designed to authorize equitable payment for your medical services. We believe this is realistic and essential if the Public is to be assured high quality care and to fulfill the intent of the 89th Congress in adopting Title XIX, namely, that "there be provided one class of service for all—the best—and the elimination of 'Welfare Medicine'." The meager provisions by the State, up to the present, have necessitated extensive charity on the part of special voluntary groups, Foundations and physicians giving their services to the indigent. It is now the philosophy of government that the financial aspects of this burden be assumed by society generally. It is the clear responsibility of local legislators to appropriate funds which will be sufficient to achieve the desired result of improving the health care and productivity of our citizens.

As an inevitable consequence of the adoption of methods of financing under the Medicare law, emphasis is now being placed on cost analysis. Indeed, a national conference was called for the purpose of finding methods of reducing the expense of health services. The attention of the consumer is being drawn to the quality, as well as the quantity, of medical health care to which he is now considered to be entitled to as a right. Undoubtedly this will be accompanied by the setting up of standards for services whether rendered in the office, hospital or laboratory. It is said that we may soon be confronted with an Ombundsman, who will be legislatively appointed, to receive complaints of the consumer. For these reasons, the Council has authorized the formation of a committee to survey and evaluate methods for determining minimum standards of quality medical care which will be useful as guidelines in the future.

We have entered a phase of widespread review and analysis of the organization of medical services and facilities. This data will provide a basis of design for posible redistribution and realignment for the purpose of making more medical care available for more people in a more efficient manner. Extensive studies are under way in all parts of the nation. In Connecticut, these are being conducted under the Regional Medical Program for Heart Disease, Cancer, Stroke, and related diseases. This movement, although at this time is out of proper sequence in relation to Federal enactment of Medicare legislation by the 89th Congress, has considerable momentum. It deserves the interest and attention of the entire Profession. It has been recommended that members of the Society actively participate and help give direction during the planning phase. Several members have already been appointed to serve on committees assigned to specific studies under the program.

Many of us are cognizant of the deficits and the sporadic crises of several nationally financed and regulated medical care systems, such as that in England. We can profit by their mistakes. It would seem wise that less energy be wasted on fear of encroachment of this type of socialized medicine and more of our energy be channelled to the guidance of existing forces toward the furtherance of a truly AMERICAN HEALTH SYSTEM with built-in flexibility to accomodate the diversified needs of our communities.

This has been a challenging year and it is reassuring that a dedicated person such as E. Tremain Bradley will be taking over the responsibilities of President.

I am grateful for the privilege you have given me to participate in the mainstream of action, as well as in theoretical considerations of socio-economic trends that are now influencing medical affairs. I consider it a valuable postgraduate educational experience and will apply insights I have gained wherever opportunity presents itself. I strongly urge each of you to continue to be involved in professional and civic projects and give direction to the design of that system which will ensure the best medical care for the citizens of Connecticut.

Thank you.

Respectfully submitted,

Orvan W. Hess, M.D.

REPORT OF THE SECRETARY

The net gain of members for the year 1966 was 69 members, which is slightly lower than it was in 1965. The last two years show an increase over previous years. Our total increase for the year was 179 members which is offset by transfers, resignations and deaths. It is with regret that we note that almost half of our membership loss was due to deaths. A detailed membership report for the year 1966 follows this report.

It is your Secretary's opinion, that there is now more cohesion within our State Society. Individual counties have shown marked interest in increasing membership and there seems to be more active membership participation at our county and state meetings. Last fall a Conference of State and County Officers was held and it is felt that this type of meeting is a good way to get at grass root thinking, and gives the county and state officers an opportunity to discuss mutual plans.

Respectfully submitted,

Waldo E. Martin

Membership Report Of Secretary

Fairfield County

Membership—January 1, 1966			944
New Members		27	
Less:			
Deaths	6		
Resignations	5		
Transfers	1		
Non-payment dues	5		
	17		
Net Gain			10
Membership—December 31, 1966			954

Hartford County

Membership—January 1, 1966			1,113
New Members		45	
Less:			
Deaths	10		
Resignations	10		
Transfers	8		
Non-payment dues	10		
	38		
Net Gain			7
Membership—December 31, 1966			1,120

Litchfield County

Membership—January 1, 1966			140
New Members		15	
Less:			
Deaths	1		
Resignations	1		
Transfers	2		
Non-payment dues	1		
	5		
Net Gain			10
Membership—December 31, 1966			150

Middlesex County

Membership—January 1, 1966			118
New Members		7	
Less:			
Deaths	1		
Resignations	1		
Transfers	1		
Non-payment dues	0		
	3		
Net Gain			4
Membership—December 31, 1966			122

New Haven County

Membership—January 1, 1966			994
New Members		66	
Less:			
Deaths	21		
Resignations	11		
Transfers	4		
Non-payment dues	4		
	40		
Net Gain			26
Membership—December 31, 1966			1,020

New London County

Membership—January 1, 1966			198
New Members		12	
Less:			
Deaths	2		
Resignations	1		
Transfers	1		
Non-payment dues	0		
	4		
Net Gain			8
Membership—December 31, 1966			206

Tolland County

Membership—January 1, 1966			26
New Members		4	
Less:			
Deaths	1		
Resignations	0		
Transfers	0		
Non-payment dues	0		
	1		
Net Gain			3
Membership—December 31, 1966			29

Windham County

Membership—January 1, 1966			73
New Members		3	
Less:			
Deaths	0		
Resignations	1		
Transfers	1		
Non-payment dues	0		
	2		
Net Gain			1
Membership—December 31, 1966			74

Associate Members		10	
New Members		0	
Less Deaths		0	
Associated Members December 31, 1966		10	

Total Society Membership—January 1, 1966		3,606
New Members		179
		3,785
Less:		
Deaths	42	
Resignations	30	
Transfers	18	
Non-payment dues	20	110
Total Society Membership—December 31, 1966		3,675
Net Gain for year		69

Totals

Fairfield	954
Hartford	1,120
Litchfield	150
Middlesex	122
New Haven	1,020
New London	206
Tolland	29
Windham	74
Associate Members	10
	3,685

REPORT OF THE TREASURER

The financial statements prepared by Seward and Monde, auditors of the Society, are self-explanatory and are respectfully submitted as the report of the Treasurer.

After reporting for six consecutive years that the surplus funds of the Society were being depleted, we are pleased to report that the trend has finally been reversed and that this year we were able to replace some of the previous depletions. When the Budget Committee was preparing the 1966 Budget, it was realized that the surplus funds of the Society were down to about one-half of the desired level of reserves and it was for this reason that a dues increase was recommended in 1966. The dues increase and a sizeable increase in advertising income are the two major factors that made this replacement possible.

It is considered good business practice to hold in reserve the equivalent of at least one year's anticipated income. On this basis we are still about twenty-five per cent short and it is hoped that with prudent management, we can reach the desired objective.

Respectfully submitted,

Isadore S. Goldberg, M.D.
Treasurer

REMARKS BY E. TREMAIN BRADLEY, M.D.

At Inauguration As President Of The Connecticut State Medical Society

Mr. Speaker, Dr. Hess, Members of the House, Welcome Guests:

In my first words to you as President of the Connecticut State Medical Society, I wish to make certain acknowledgments. I wish to express my appreciation for the opportunity of serving you for the forthcoming year. Your Council has been most tolerant of my searchings—encouraging, sometimes sobering, even permissive. In undertaking this work, I have relied heavily upon the fund of knowledge, the limitless energy and the genuine cooperation of our General Manager, Dr. Richards. And I am grateful and bounden to Dr. Orvan Hess, who as President this past year has befriended me and been most generous in cooperating with the changes which were started today in the modus operandi of the House of Delegates and which we hope to see progress much further next year. I hope you appreciate, as I do, his consideration of all points of view, his impartial judgment, and his fine leadership.

The world today is full of change. Is this progress or regression? Our federal father is fostering a "Great Society." Our sister state is sponsoring a "Just Society." As Orvan Hess says, we physicians in Connecticut want a "Just Great Society." It is obvious that we cannot continue according to pattern because of all the forces which are brought to bear upon the practice of medicine. Some of these are intrinsic and some extrinsic. Perhaps this is the time to stand back and appraise objectively the job which needs to be done and what we have to do it with, not being unmindful of history and yet not overly prejudiced by it.

Today's physician is blessed, and burdened, with a vastly expanded science of medicine. He suffers from the pressures of complicated diagnoses and the intricate processes of directing treatment. Our scientific advances and excellent medical care of patients has precipitated a socio-economic crisis. We must certainly undertake the role of efficiency expert in apportioning the scarce medical personnel so as to give optimum care for all.

Are we seeking for immortality of the body along with the soul or when does the soul leave the body? To what extremes must we go—urged by our conscience, or the conscience of the elderly patients' family, or the threat of the law—in continuing the physiologic performance of the body a few extra days or weeks or hours—to the financial destruction of the relatives? Does not an individual have a right to die with dignity?

External pressures also confront us. Unfortunately, the series of political moves over the past few years were not designed primarily for the benefit of the patients but rather as power plays. In Congress now is House Bill 5710 containing various amendments to the Medicare Bill (too bad the basically good Kerr-Mill's Law was not accorded a similar courtesy!) All members of the Society have received comments about the various parts of this Bill. They warrant your immediate attention—and action! Each of us should select two or three items which are of particular interest. Then write your two Senators and the Representative from your area about them. Your letters will receive much more attention than they did last time.

We must be sure to have physician representation on all committees and commissions involved in health care so that the true facts can be presented and the interest of the patients can be protected. We must try to take an unprejudiced look at the whole situation, hopefully coming up with constructive and practical thoughts.

The onslaught of the campaign of the lay press to undermine the public's confidence in doctors seems to be losing momentum. Could this be at least in part because organized medicine has stopped worrying about public opinion at every turn and has proceeded with what seems best? We must have clear thinking. Then we must have courage. No one can destroy the dignity of the medical profession—unless it be the profession itself and this is indeed unlikely. Of course, nobody is perfect. Every group is apt to have some 'bad boys" in it, and the medical profession is no exception. But by and large when it comes to the giving of time, energy, and self, in the service to his fellow man, the physician stands about at the top of the list.

Long before the popular literary game of discrediting the doctor, and before the politicians started vying to establish the highest standards of health care, the medical profession had instituted auditing systems to improve and make more efficient a system of delivery of medical service unequaled in the world, a system unfettered by government fasces—statutory and financial. Medical service is from *one* human being to *another;* it should not be categorized, nor so remunerated. Impatience and pressures from non-professionals may result in too-hasty stream-lining. We must cope with whatever the facts are and continue our efforts to improve the situation.

If, after these remarks, you are confused, that puts us *all* in the same boat. Let each and every one of us dip our oar in. There will be some crabs caught and a bit of splashing, but the boat will generally move up-stream to new scenery and fresher water.

Challenge may be the cornerstone of progress but as you see, progress now presents a challenge. Do you accept it?

Discuss in your local and county medical associations the problems which you see in practice, and send these on to the House of Delegates for discussion in a reference committee. The resolution can be simply for study, with or without recommended action. In these times of doubt, insecurity and struggle, we doctors—individualists that we all are—must pull together. It would be indeed unfortunate if it became necessary for the physicians of this country to band together to form a federation. I believe in the integrity of the doctors and the intelligence of the people of this country.

OBITUARIES

Charles Lewis Larkin, M.D.

1889 - 1967

Dr. Larkin, attending gynecologist at the Waterbury Hospital and St. Mary's Hospital in Waterbury, died suddenly of a coronary occlusion in Inverness, Florida, on February 8, 1967.

Dr. Larkin was born in Waterbury on March 31, 1889. He graduated from Crosby High School in 1908; received a B.A. from Yale University in 1912; M.D. in 1915. He had internships and residencies in surgery at St. Luke's Hospital, New York, 1915-17; in gynecology at Roosevelt Hospital, 1917-18; and in obstetrics at Fordham Hospital, 1919. He was in the United States Army Medical Corps from August, 1917, to November, 1918. He was licensed to practice in Connecticut in 1919, when he opened his office in Waterbury, specializing in obstetrics and gynecology.

Dr. Larkin had a large practice, with many devoted patients in whom he took a great deal of personal interest. The fact that his personal kindnesses are remembered by so many is an eloquent tribute to the deep concern he showed for the welfare of his patients beyond their illnesses. After maintaining an office for many years on North Main Street, Dr. Larkin built the Larkin Clinic on Chase Parkway in 1954. He continued to see patients at the clinic up until shortly before his death, although he had retired from active surgery two years earlier.

Coming to Waterbury from the Army and the New York hospitals, Dr. Larkin was deeply interested in both the Waterbury Hospital and St. Mary's Hospital, and put a great deal of effort into staff organization, hospital procedures, and the educational programs which contributed to the raised standards and eventual accreditation of both hospitals. He was president of the staff at St. Mary's Hospital in 1947 and of the Waterbury Hospital medical staff in 1950.

As an outgrowth of his type of practice, Dr. Larkin early became interested in the problem of malignancy and was a founder of the Connecticut Cancer Society of which he was a past President. In 1952, Dr. Larkin was awarded the Gold Medal of the American Cancer Society for his "significant contribution to the control of cancer."

Dr. Larkin was active in the Waterbury Medical Association and was President in 1948. For many years he successfully guided the financial policies of the Association. He also belonged to many other medical societies and organizations. Among these were the New Haven County Medical Association, the Connecticut State Medical Society, the American Medical Association, the New England Surgical Society, the New England Gynecological and Obstetrical Society, and the New England Cancer Society. He was a diplomate of the American Board of Obstetrics and Gynecology and a Fellow of the American College of Surgeons.

Dr. Larkin was highly regarded by his colleagues as an original, resourceful, and skillful surgeon. Throughout his life he was always modest, genial, and unassuming, and had a delightful sense of humor.

He was quite an athlete in his earlier years, a strong competitor, and was on the Yale track team in college. He kept up his golf and tennis until very recently.

Dr. Larkin was helpful to many newcomers in the profession in Waterbury and many of us had a warm and lasting appreciation over the years for the encouragement, advice, and help in those early days. He will be remembered as one of the most colorful members of a long line of eminent Waterbury physicians.

The aforementioned accomplishments indicate the many contributions made by Dr. Larkin to the Connecticut area both in medical and in community affairs. Dr. Larkin was indeed a remarkable man.

John H. Foster, m.d.
Albert E. Herrmann, m.d.

Francis L. Lundborg, M.D.

1902- 1967

Dr. Francis L. Lundborg, 64, of 35 North Main Street, West Hartford, Connecticut passed away at the Hartford Hospital on April 16, 1967.

Born in Central Falls, R. I., he lived in West Hartford most of his life. Graduating from Hartford High School he went on to Trinity College and received his B.S. degree in 1924, his M.S. degree the following year, and then his M.D. degree from Yale Medical School in 1930. He then interned at the Hartford Hospital and entered private practice in 1932.

Dr. Lundborg's professional life was largely devoted to Trinity College where he did an outstanding job which won him the high esteem of many generations of students, and the respect and affection of his academic colleagues. At first his service to the college was part time, during which he was also in private practice. In 1934 he became assistant medical director and in 1948 medical director.

During World War II he served as a Captain in the Army Medical Corps, as an army surgeon both in the United States and France.

His life was beset by many unusual physical difficulties which required many prolonged and serious hospitalizations. Through these experiences he maintained equanimity and good humor. He was a good father with three fine sons, one of whom has followed him into medicine and will graduate from medical school this June, and then intern at the Hartford Hospital. Dr. Lundborg knew of this before his death and was proud of this son as he was proud of the achievements of all three of his children.

Always a good fellow, he loved bridge and played this game with an all out brilliance quite disconcerting to his fellow opponents. His friends and Trinity College will miss him.

He leaves his wife, Dorothy May Lundborg, always staunch and loyal; three sons Francis L. Lundborg, Jr., Richard Dodge Lundborg, both of West Hartford and Carl B. Lundborg who will shortly be adding the suffix, M.D. to his name; a brother Walfrid G. Lundborg of Farmington and a sister Miss Edda E. Lundborg. He was a member of St. James Episcopal Church, West Hartford, the Hartford Hospital Staff, the Hartford County Medical Society, the Connecticut State Medical Society and the American Medical Association.

Lewis A. Griffin, M.D.

Edwin R. Connors, M.D.

1904 - 1967

Dr. Edwin Connors, medical director of the Connecticut State Welfare Department, died at his home in Hartford March 18, 1967.

Born June 3, 1904, in Stonington, Connecticut, he was a graduate of Providence College and received his M.D. degree from Boston University School of Medicine in 1931. He interned at Bridgeport Hospital 1931-1932, after which he started general practice in Bridgeport. He was a senior attending and the first chief of the general practice section, which he helped organize at Bridgeport Hospital. He served in the Army Medical Corps with the rank of captain from 1942 to 1943. He was past president of the Bridgeport Hospital staff.

He was a past president of the Bridgeport Medical Association. In 1953, he was president of the Connecticut Academy of General Practice and had been a member of its board of governors since 1948. He was a member of the Fairfield County Medical Association and served as its secretary from 1949 to 1955 and was a member of its board of trustees. He was a transfer member to the Hartford County Medical Association and a member of the Connecticut State Medical Society and the A.M.A.

While in Bridgeport, he was medical examiner for East Bridgeport from 1951-1960. He was a member of the Knights of Columbus, St. Lukes Physician and Dentist Guild, the Fairfield County Medical Golf Association and the Association of Medical Examiners of Connecticut.

In 1960 he was appointed medical director of the State Welfare Department where he served until his death.

During the last days of his life, Dr. Connors concern was for his family and friends. He knew the nature of his illness but he continued to do his work as long as he was physically able. Among his last words to me about his enforced idleness were, "What a waste of time."

Working and helping others was a way of life with Dr. Connors. Many of the younger doctors in the Academy of General Practice will remember the help and advice he gave them when it was needed most.

Dr. Connors started his general practice in Bridgeport in the difficult days of the "early thirties." He loved his work and was rewarded by the affection of his patients. I believe that the conditions which Dr. Connors found in those depression years later helped him to decide to leave his practice and move to Hartford. He became medical director of the State Welfare Department where he used his executive ability to procure good medical care for the needy. During the seven years which he served as medical director, his abilities were recognized by his superior, by his staff and medical directors in many parts of the country.

I was privileged to know Dr. Connors as a classmate, family physician and friend. His loss will be a great one to his beloved wife, Ruth, and devoted sister, Mary, and to his many friends in the profession. We shall remember his good service and cherish his memory.

NICHOLAS E. CREATURO, M.D.

In Memoriam

Davis, Thomas F.—Bridgeport; Tufts University School of Medicine, 1921. During World War II, Dr. Davis was chairman of the Medical Aid Services Division of the Fairfield Defense Council. He was the physician at Fairfield Preparatory School and Fairfield University. He was also chairman of the Fairfield School Board. Dr. Davis was associated with St. Vincent's Hospital. He was a member of the Fairfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Davis Died April 14 at the age of 69.

Rogowski, Bernhard A.—New Haven; Yale University School of Medicine, 1924. Dr. Rogowski was a practicing psychiatrist in the New Haven area for over 30 years. He was an associate professor emeritus of Clinical Neurology at the Yale University Medical School. He was a member of the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Rogowski died April 14, at the age of 66.

Tate, William—Deep River; Yale University School of Medicine, 1929. Dr. Tate had practiced in Deep River for over 35 years. During World War II he was a captain in the Army Medical Corps. Dr. Tate was one of the founders of the Deep River Ambulance Association and has been a director for the past ten years. He was on the medical staff at the Middlesex Memorial Hospital. He was a member of the Middlesex County Medical Association, the Connecticut State Medical Society, and the American Medical Association. He was also a member of the Middlesex County Heart Association. Dr. Tate died April 29 at the age of 63.

Around The State

New Haven County

The first meeting of the New Haven County Medical Association Board of Governors since elections held at the Annual Meeting in March, took place at the Colonial House in Hamden Thursday, April 20, 1967, at 4:30 P.M. Dr. Bernard Burnham of Waterbury was elected chairman of the Board for 1967-68.

The business of the meeting had to do largely with resolutions which will appear on the agenda of the annual meeting of the House of Delegates of the Connecticut State Medical Society, April 25, 1967. Some of these have originated in our Board of Governors.

Briefly listed, one of our resolutions asked the House to urge the State Board of Health to allow any qualified physician who has privileges to perform gynecological surgery to admit clean gynecological cases to the obstetrical ward. Another dealt with the "usual and customary fee" as paid by Welfare Commissioner Shapiro. It was called a paradox and we went on record opposing any fee schedule that is used to implement Title XIX. Two other resolutions dealt with the question of Specialists' Professional Services and prescribing by generic terms.

A complete report of our Annual Meeting was submitted by the Clerk and Committees were appointed by Dr. Burnham as specified in the By-laws.

The meeting was followed by the usual social hour and dinner.

Respectfully submitted,

H. A. LEVIN, M.D.

MEDICAL NEWS

Physician Responsibility In Preventing Suicide

The physician has both an opportunity and responsibility to prevent many suicides, says the current Journal of the American Medical Association.

Because many disturbed people see a physician for some real or imagined physical complaint before attempting suicide, the doctor has a chance to observe their condition and take action to help save their lives.

The physician walks a fine line, however, between his ethical responsibility to preserve the patient's privacy when the threat of suicide is not serious, and his responsibility to save life when it is.

This responsibility for taking preventive action in suicide threats is an added role for the physician, one he has been asked to assume only recently, notes a Journal editorial.

One Journal report presents a Boston psychiatrist's multistep test for determining the seriousness of a suicide threat. The physician's responsibility for preventing suicide increases with each indication that the patient's threat is serious, said Philip Solomon, M.D., of the Boston City Hospital psychiatric service and Harvard Medical School.

A second Journal article by two St. Louis psychiatrists notes that alcoholics who have recently lost a loved one are particularly vulnerable to suicide. They report that among 31 consecutive alcoholic suicides in an urban area, nearly half the deaths occurred within a year after the loss by death, divorce, or separation of someone close to the victim. The majority of these suicides happened within six weeks of the loss.

It is impossible to prevent many suicides, partly because the triggering emotional crisis cannot be anticipated. It is possible, however, to determine when a person is alcoholic and to anticipate such crises as divorce and separations, said the authors, George E. Murphy, M.D., and Eli Robins, M.D., of the Washington University department of psychiatry, St. Louis.

"Probably most normal people have had suicidal or homicidal thoughts at some time in their lives," Dr. Solomon said.

When they talk about these in the doctor's office, it may not be serious at all. But when the doctor asks, "Have you thought about *how* you would do it?" and if the patient has some positive answers about sleeping pills, jumping, drowning, shooting, etc., then further questioning is called for, Dr. Solomon said.

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Therapeutic Effects: Tandearil is a nonhormonal compound which may rapidly resolve inflammation and help restore normal joint function. Its action does not affect pituitary-adrenal function or impair immune responses. Its value in osteoarthritis is especially noteworthy because this disorder responds inconsistently to steroids and is often resistant to salicylates. Further, indomethacin is limited only to osteoarthritis of the hip, whereas oxyphenbutazone is effective in all forms of the disease.

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage. Make regular blood counts. Discontinue the drug and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: The initial daily dosage in adults is 300-600 mg. in divided daily doses. When improvement occurs, dosage should be decreased to the minimum effective level; this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

For complete details, please refer to full prescribing information. 6562-VI(B)R

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ANNUAL REPORT OF THE PRESIDENT — MAY 25, 1967

If I may beg your indulgence for a brief moment, I would like to relate a brief bit of humor that has a direct relationship to my report to you.

Do you recall the recent cartoon in *News Week* magazine appropo to an article on the difficulties of a contemporary college education, called "The Pressure Cooker"? The cartoon depicts an anxious father at the telephone (and I'm sure those of you who have or had daughters or sons in college will appreciate this); Mother is coming down the stairs, hand clutched to breast, other hand clutching the stair rail as father says "Listen to me Francine, stay in Wellesley, we will discuss 'Who you are and who I am' over the vacation."

As to who YOU are, Your Auxiliary believes (to borrow from the vernacular) YOU are "THE MOST," YOU are our "raison d'etre."

Now . . . WHO ARE WE? Your Auxiliary is an organization of 1,141 women whose primary objective is to assist the Connecticut State Medical Society in its program for the advancement of medicine and public health.

Through the various scholarship committees in the County Auxiliaries, thousands of dollars are raised each year and given in direct grants to medical students, student nurses, and A.M.A.E.R.F.

Through the Legislative Committee we support those bills which your Legislative Chairman asks us to support and register our protests to that legislation which is not in the interest of good medicine and good health.

Our International Health Committees send hundreds of medical books and periodicals to the "Darien Book Plan" for distribution overseas, along with making knitted and torn sheet bandages for leper colonies.

Our auxiliary is offering a scholarship to an educator in the health field to attend the graduate session at the University of Connecticut, the course being called "The Family Institute," with an emphasis on sex education.

County Auxiliaries sponsor "Health Career Days" in the schools and distribute literature pertaining to health careers.

In the community service fields we distribute "Meals on Wheels" to the elderly, conduct preschool visual testing clinics, and have various projects for the patients in mental hospitals.

I have merely skimmed the surface of "Who we are and what we do" as YOUR Auxiliary.

We are here, ready and willing to help as YOUR AUXILIARY, but may I ask you to HELP US to HELP OU.

I believe every physician's wife whose husband is a member of the Connecticut State Medical Society should be a member of the Woman's Auxiliary. Wont you PLEASE ask your wife TODAY, if she is a Member of the Auxiliary, and IF NOT, WHY NOT?

We are your "True Friends in Court."

Thank You,
Mrs. John D. O'Connell,
President

It's your professional privilege to replenish your ranks . . .

Give to medical education through AMA-ERF

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Connecticut State Medical Society
SCHOOL HEALTH NEWSLETTER

No. 2 June 1967

What About Sex Education

This is the second of a series of three newsletters on school health subjects which has been authorized by the council for publication in the Journal. Reprints of each issue will be made available to the State Commissioners of Health and Education for distribution to personnel within their respective departments.

This page is directed at all Connecticut physicians since all of you, like it or not, have a stake in education for health. If you don't believe it, read on and think.

This newsletter is for you. It will note, highlight, and review events, experiences, and publications pertinent to the health of school children.

Physicians do not realize that modern school health programs are far more than mere inspection of partly clothed bodies. A good school health program must include (1) proper public health and sanitation in the school plant; (2) health education; (3) the screening for physical defects; (4) proper physical education; (5) provision for a healthy emotional atmosphere; and (6) programs adapted for the handicapped child.

Basic Facts

1. *Connecticut Facts*

   According to State Department of Health figures and estimates, it is concluded that in the years of 1963 and 1964, one (1) in eight (8) Connecticut girls gave birth to an illegitimately conceived live baby prior to reaching age 20.

   In addition, an unknown number of teenage girls experience an out-of-wedlock pregnancy that fails to terminate birth of a live born infant.

2. 50% of all teenage marriages end in divorce.

3. Modal marriage age for—college graduates—22 years:
   high school graduates—18 years;
   non high school graduates—14-16 years.

4. Out-of-wedlock teenage pregnancy usually marks the beginning of a destructive cycle consisting of failure to continue education, dependency on the State Welfare System, lack of stable family life, and continuing the reproduction of illegitimate offspring. Also it increases the incidence of obstetrical problems as toxemia, obesity, prematurity and perinatal mortality.

5. *Sex Education Pays Off.*

   In a Washington, D. C. study in 1960, a sex education program in a Junior High School effected a drop in teen pregnancies from 38 reported in 1959 to 17 in 1960. A similar statistically significant drop in the evidence of venereal disease was reported.

Food For Thought

1. *What is Sex Education?*

   Sex education is the development of attitudes that view the fundamental differentiation of the male and female sexes (biological, psychological, and social) as involving the whole person. It establishes a set of values, acceptable from a personal, social, moral, and religious aspect, to "aid humans (Siecus) toward the responsible use of the sexual faculty and towards the assimilation of sex into their individual life patterns as a creative and recreative force."

2. *Why the need for Sex Education?*

   a. Parents and teachers lack any clear concept of the outcomes they hope to achieve with sex education for youth beyond "keeping them out of trouble."

   b. Changing attitudes towards previously accepted moral values; the number of homes broken by death, divorce, or separation; lack of adequate housing; modern developments in urbanization; increasing mobility of population; delinquency; population explosion.

   c. The educational status of the average parent today is something less than that of a eighth grade level.

   d. Adolescence is normally a period or resistance to parents, and, adolescents rarely turn to them for advice and direction.

   e. By and large, youth 'educate" each other.

3. *Shared responsibility.*

   A Sex Education program is a shared responsibility of the school, home, and church.

4. Sex Education Programs should be uniform and comprehensive in the teaching of family life material and reproductive physiology at appropriate ages.

Research

A New Haven, Connecticut Study by Dr. Phillip Sarrel revealed the following:

a. 123 illegitimate pregnancies occurred in a 24 month period to patients 17 years or younger (1959-1960).

b. In addition to the original 100 babies, this group of mothers had 240 more babies and 9 abortions in the following five-year period.

e. Only 9 of 36 girls who had married are still living with their husbands.

Physicians Role

1. Increased knowledgability in human sexuality for more effective counseling and education of their own patients.

2. Inform schools of their interest in this field.

3. Be available as resource personnel and consultants to schools (i.e., the Hamden, Connecticut Public School Health Education Program).

Quite suddenly, many towns are moving in the area of sex education. What's going on in your town?

References and Recommended Material

Connecticut Health Bulletin, January, 1967
Journal of School Health, Milton I. Levine, January, 1967
Connecticut Health Bulletin, July, 1966
SIECUS Newsletter, Summer 1966
Journal of School Health, Kinhendall and Calterwood, September, 1965
Publications by Planned Parenthood Association on Sex Education, New Haven Office
Sex in the College Student (Published by the Group for Advancement of Psychiatry)

Films

1. Phoebe (the O-W problem)
2. Human Growth (available from State Department of Health)
3. Human Reproduction
4. Population Ecology

If you have read this material, thought about it and like it or are critical, let us know.

Advisory Committee on School Health
Connecticut State Medical Society
Joseph J.. Bellizzi, M.D., Chairman

Prepared for publication by the Connecticut State Medical Society Advisory Committee on School Health.

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Air Pollution's Effects On Runners

The motor-fuel oxidant type of air pollution in the Los Angeles area may hamper athletic performance, suggests a report in the current Journal of the American Medical Association.

High school cross-country runners at San Marino, Calif., a Los Angeles suburb, performed poorest at track meets when oxidant air pollution was greatest during the six-year period, 1959-1964.

The Los Angeles area's oxidizing type of air pollution is caused by photochemical reactions with motor fuel. It isn't known, the Journal report said, whether this type of smog had a direct physiological effect on the runners, or whether it simply decreased their motivation by causing chest discomfort, a frequent complaint in smog areas.

The report, by researchers from the U. S. Public Health Service and the University of Southern California School of Medicine, also stressed that this study applied only to Los Angeles' oxidizing type of air pollution.

The study started with records of runners' performance kept by San Marino track coach Jack Bradford. Long-distance runners ordinarily would be expected to perform better as the season progresses. According to Coach Bradford's records, however, many runners failed to improve their racing times, or did not improve as much as expected during certain track meets.

When the dates of these meets were compared with records of the Los Angeles County Air Pollution Control District, it was found that poorest running performance coincided with periods of greatest oxidizing air pollution near the high school track.

Other factors, such as temperature, relative humidity, wind velocity and wind direction showed no correlation to runners' performance. Correlations were less striking or absent with other measures of air pollution, such as concentrations of air-suspended particles, carbon monoxide, or oxides of nitrogen.

Because the runners were at sea level, where oxygen is plentiful, it seems unlikely that performance was decreased by oxygen lack, the report said.

"Oxidizing pollution is definitely irritating to the eyes, and athletes often complain of chest discomfort after exercising in the Los Angeles area on days with high pollution," the report said.

The authors are Walborg S. Wayne, M.S., and Robert E. Carroll, M.D., M.P.H., of the National Center for Air Pollution Control, U. S. Public Health Service, Cincinnati, Ohio, and Paul F. Wehrle, M.D., of the University of Southern California School of Medicine and the Los Angeles County General Hospital, Los Angeles.

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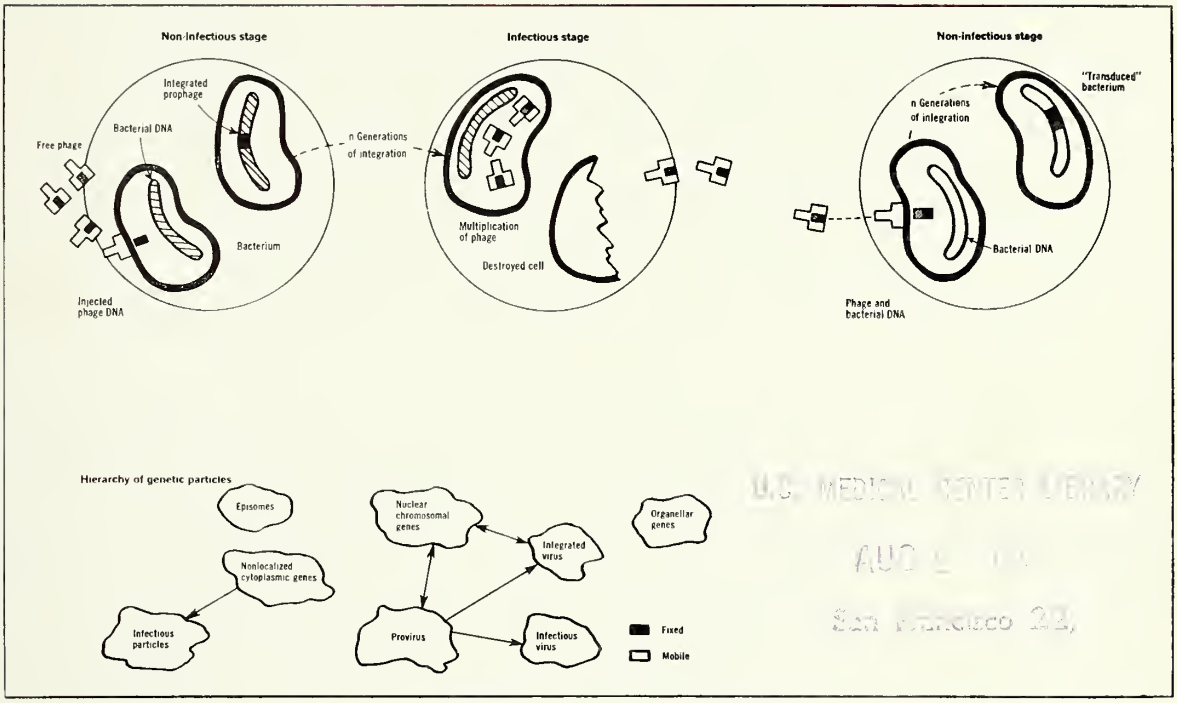

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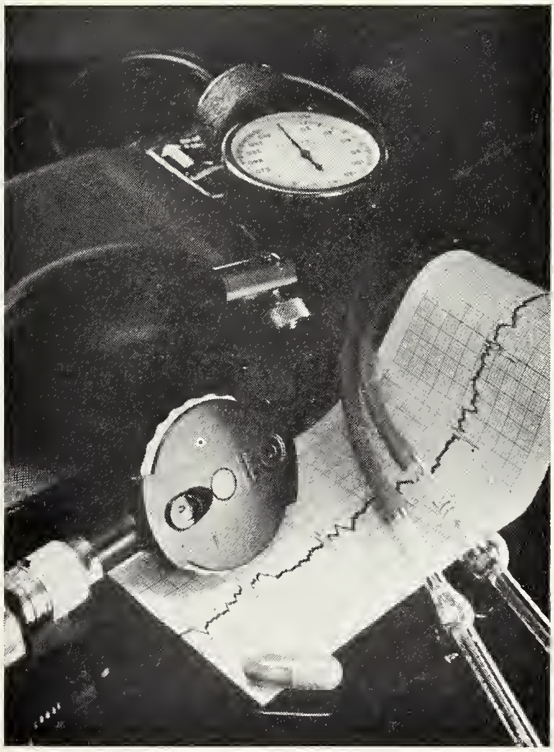

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Connecticut Medicine

editorials

Genes, Heredity And Infection

Three months before Peyton Rous was awarded the Nobel Prize for his discovery of a chick cancer virus, Eleanor Alexander-Jackson published her hypothesis that the famed Rous Virus is really only a virus-like form of an exotic type of bacteria—mycoplasma. Her experiments covered a four year period during which she repeatedly isolated mycoplasma type bacteria from Rous virus cultures. This isolate was definitely not a contaminant since it induced a Rous cancer-like disease in chickens.

This led her to the view that Rous virus is not a virus at all but rather a virus-like, virus form of a pleomorphic organism mycoplasma which belongs to a special bacterial Order Actinomycetales. In its "normal" state this Order has been known to simulate several different species of bacteria such as micrococci bacilli and even certain types of fungae. The Rous virus is a type of bacterium which is peculiar because it reverts to a mycoplasma by shedding its rigid wall and producing colonies of fungus like cell communities surrounded by a single cell wall.

This raised two questions. One is whether all viruses are simply transitional or alternative forms of other organisms. The second is whether they constitute a separate category of life in the sense of an animal or plant species, or do they originate normally from the normal constituents of living cells. Clearly the answer to these questions will come when we know more about bacteria which propagate both by heredity and also by infection (see front cover).

It is known that most species of bacteria found in nature are subject to infection by specific viruses termed "phage" which arise usually from individuals of their own species. If all bacteria were susceptible to phage infection, then phage would work its way through the whole bacterial population, destroy them and the liberated phage would forever vegetate and itself ultimately die. This is not what happens in nature. In each bacterial species there are some with resistant genomes in which the phage enters, takes up residence in a non-infectious state, the prophage, and divides as the cell divides for many generations. It assumes a specific location on the bacterial chromosome becoming one of its genes. The shift from non-infectious prophage to infectious phage can be initiated by X-rays, reducing agents, radiation that damages the chromosome. The phage itself can become defective by mutation so that a mature phage cannot be produced.

Since the prophage can be viewed as a fragment of the hosts genetic message entirely capable of initiating its own multiplication, given a cellular laboratory for synthesizing protein, we are permitted to construct a hypothesis that possibly all viruses may originate from the normal constituents of the cell. If this be true the next question is how would a propensity of bacteria to produce phage be of benefit to bacterial populations in a genetic and evolutionary sense.

A coherent scheme to explain this strange association was drawn up by Darlington in 1958.[3] It rests on the phenomenon of bacterial transduction frequently observed in salmonella and Escherichia. In these strains, the phage produced by one strain can infect another strain, thereby changing the genetic make-up of the infected strain. The phage of course can multiply by itself and destroy the strain, but if it is successfully integrated, it will become a part of the hereditary mechanism of the new bacterial cell. It becomes a sort of mixing of genes by pairing of different mating types. This exchange of genetic material occurs as it does in sexual reproduction, and is responsible for adaptation and production of many new forms.

Darlington points out that there are proviruses in certain plants as for example being responsible for certain brilliant colors in tulips. There are also proviruses termed plasmagenes in species of moths and King Edward potatoes. They play a normal part in the cytoplasm, not nucleus of larger organisms, but also have the capacity of multiplying and diffusing in an infectious state, as well as a state of integration and not infection. They can however be made infectious by treatment similar to making phage infectious and thereby lead to the death of the host.

This distinction between provirus and virus, according to their mode of transmission, the first by heredity, the second by infection, is extremely important from the evolutionary point of view, where the provirus is balanced in its propagation, it benefits its host and permits adaptation.

It is clear from the above that there are several fundamental genetic agents related to cellular function which are molecular in scale and have a capacity for self-propagation. Some like the elementary particles in physics disappear, reappear and transform from one to another. There are the nuclear genes found in the chromosomes of cell nuclei and the central core of DNA or RNA viruses and phage. Then there are the organellar genes, inside the cell protoplasm such as plastids that carry on photosynthesis in plants, Kappa particles —virus-like lethal agents, and gullet apparatus of paramecium and even the mitochondria (bodies which mediate respiration in animal cells.)

There are also non-localized particles which do not seem attached to known structures but are fixed in the cell where they originate. They pass through the egg in heredity. Examples are non-chromosal resistance in certain green algae to streptomycin and inheritance of non-chromosomal male sterility in maize. In the mold Podospora, the nature of their mycelia is controlled by a non-chromosomal maternal factor that can also propagate by infection.

The distinction between provirus and virus according to their mode of transmission, the first by heredity and the second by infection, is extremely important. It lends some intelligibility to the evolutionary relationship between viruses and other organisms although it does not explain the relationship between the Rous virus and its bacterial form. But it does suggest that the virus particle may actually arise from the normal constituents of some cells. Under certain conditions it can add new genetic information to other cells. Under different conditions it can also infect and destroy.

L.H.N.

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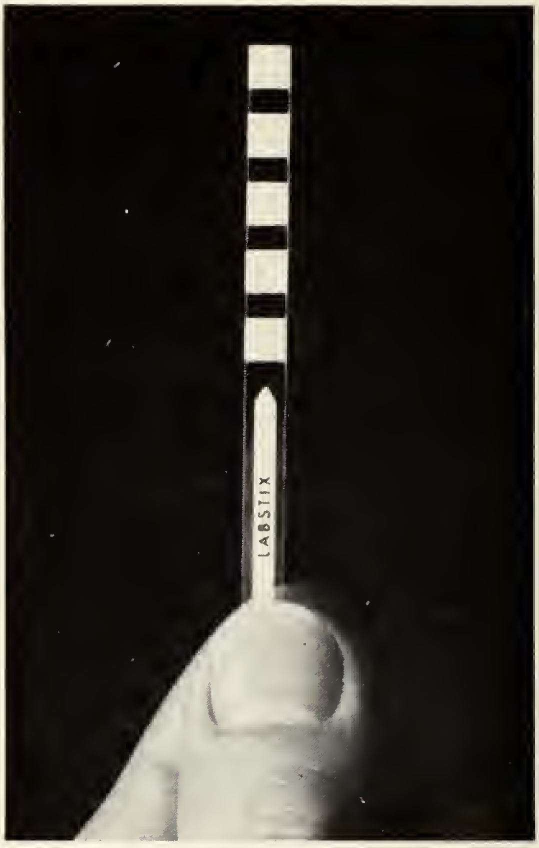
Bioamines And Emotion: I. Peripheral Effects

Long ago Walter B. Cannon, then professor of physiology at Harvard suggested adrenalin was secreted in response to stimuli which produced fear and rage reactions in animals. Two views about affective states developed; one was that it was the visceral response that created the affective sensation in animals and the other that visceral responses



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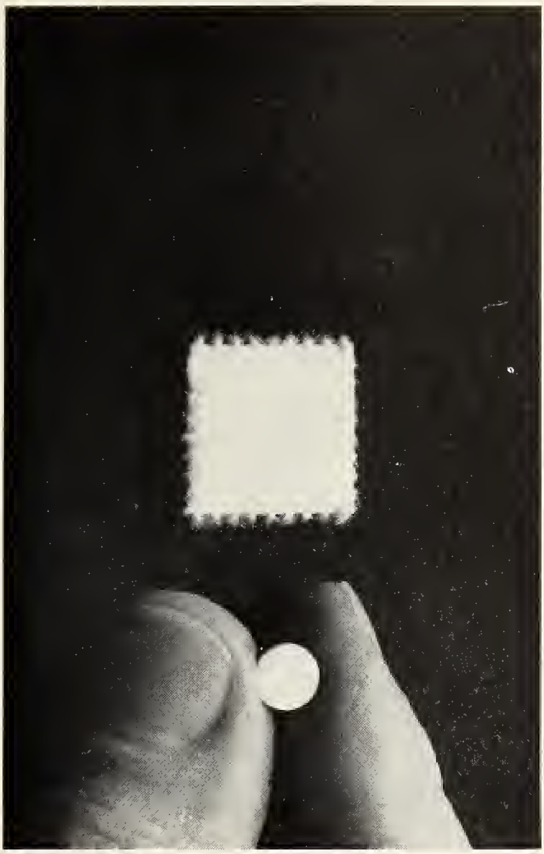

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were only part of the whole problem and the central nervous system was the prime factor.

Since Cannon's day the physiology and metabolism of the biogenic amines have been studied in various affective states including normal and physiological anxiety, depression, elation and anger. Research in this area was further stimulated in the past decade by the finding that many of the drugs used in the psychiatric treatment of patients with affective disorders also cause significant changes in the metabolism and function of various biogenic amines both peripherally and also centrally.

Norepinephrin, dopamine, indolamine, serotonin are the brain mono-amines on which interest has focused. The highest concentration of norepinephrin is found in the hypothalamus although it is also distributed in many other areas. Compared to norepinephrin, epinephrin occurs in very low concentrations. Dopamine which has recently been implicated in Parkinson's Disease, is found in highest concentration in the basal ganglia but lower concentrations are also found in most other areas. Serotonin is found in high concentration in various peripheral tissues, notably the gastrointestinal tract, but it is also found although in lower concentrations in the brain in appreciable amounts being similar to norepinephrin in its distribution.

By a histochemical fluorescence method monoamine neurones have been identified. High densities of such neurones have been found in the limbic system which of course includes the hypothalamus and other functionally related brain structures which may be concerned with emotion.

The role of norepinephrin as a chemical transmitter at the receptor sites of the peripheral sympathetic nervous system is well established. What its role is in the central nervous system is now in the process of clarification. One thought is that it assists in generating a nerve impulse at the junction of two adjacent neurones by being released at the presynaptic nerve ending. Another thought is that norepinephrin, dopamine, and serotonin may each function directly as a transmitter substance in the central nervous system. A third thought is that one or more of these amines may act as modulators or regulators of synaptic transmission which is really mediated by some other chemical transmitter such as acetylcholine.

Norepinephrin is found to be secreted at sympathetic nerve endings while epinephrin comes almost exclusively from adrenal medullary secretion. Norepinephrin does not cross the blood brain barrier. Therefore the brain cannot furnish circulating norepinephrin. Neither can peripheral norepinephrin be a source of brain-epinephrin. Obviously norepinephrin is a product of neuronal synthesis whether we find it centrally or peripherally.

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There is much evidence that physiological responses during anger resemble reactions to an injection of norepinephrin alone whereas responses of the organism during fear seem to resemble those induced by an injection of norepinephrin and also epinephrin. Anxiety and depression however caused cardiovascular responses similar to those observed during epinephrin infusion.

In the rhesus monkey increases in blood levels of epinephrin occurred in situations which combined uncertainty and unpredictability with the threat of noxious stimuli and anticipation of the need for coping behavior. On the other hand if the situations associated with administration of noxious stimuli were familiar and predictable then release of norepinephrin occurred. In short work performed under conditions of stress, then improved performance led to increase production of norepinephrin.

Such data seem generally compatible with the hypothesis that psychological and situational factors differentially affect the relative production of norepinephrin and epinephrin. That increased epinephrin secretion seems to occur in states of anxiety or in threatening situations of uncertain and unpredictable nature in which active coping behavior may be required but has not been achieved.

In contrast norepinephrin excretion may occur in states of anger or aggression or in situations which are challenging but predictable so that they allow active and appropriate behavioral responses to the challenge.

Peripherally then increase of either epinephrin or norepinephrin or both of these catecholamines may represent specific adaptive responses to varying external conditions. It is in this area where psychosocial, biochemical and physiological investigation may be particularly rewarding. Since adrenocortical steriods enhance the activity of enzymes which convert norepinephrin to epinephrin in the adrenal gland we may from further study learn the functional inter-relationships of these hormones in man.

Infusion of epinephrin in human subjects has led in some to feel as if they were anxious, but in others no emotional changes. This was found even less often with administration of norepinephrin. Schachter and Singer[3] in one of the few studies in which environmental factors have been controlled, have shown that in experimental situations designed to produce either euphoria or anger, then the mood could be accentuated by administration of epinephrin but not by a placebo.

The question remains whether epinephrin administered or released peripherally produces changes in affective states by direct action on the hypothalamus or through subjective perception of ts peripheral effects, effects which "resemble" hose of anxiety. This controversy though old is ot answered: visceral origin of emotion or central erception of it.

L.H.N.

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Science Tools: 25.
Plasma Insulin In Disturbed Carbohydrate Metabolism

Impaired glucose tolerance increases with age, in pregnancy, obesity, acromegaly, thyrotoxicosis, uremia, hepatic disease and myocardial infarction. If these disorders are present the diagnosis of diabetes mellitus presents special problems. The mechanism of the associated abnormalities noted in glucose tolerance in these disorders has been considerably clarified by determinations of plasma insulin in the fasting state or during a glucose tolerance test.

Plasma insulin is now determined by a radioimmunological method (which gives the lowest but most specific estimate) or by a method which measures total serum insulin like activity (ILA) in the rat diaphragm or fat pad. In general the rise of blood insulin during the oral glucose tolerance test (OGTT) is greater but the peak value is later than that seen during an intravenous glucose tolerance test.

The reason for this apparently discrepant response to oral glucose seems to be an increase in peripheral plasma glucagon after large oral glucose loads. We know that small doses of glucogon will stimulate insulin secretion once they enter the blood stream. Several workers have emphasized that the gut produced a glucagon with insulin releasing properities just as the alpha cells of the pancreas do. If another glucagon source in the gut is stimulated to produce it by an oral glucose load then we can understand the repeated observation that glucose tolerance is better and insulin levels are higher after oral rather than intravenous glucose.

Determination of plasma insulin values reveal that in diabetes both fasting and after glucose loading, the insulin levels are higher than normal in the early and especially the obese diabetic, be-

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come lower than normal in the thin diabetic or one of longer duration and very low to absent in the juvenile diabetic. If plasma insulin levels are elevated, then it is possible to determine normal and subnormal rates of disposal of glucose during oral or intravenous glucose loading. By these technics it is possible to establish a measure of the decreased effectiveness of insulin action.

Recent large surveys show a gradual rise in blood sugar with age with no distinct or recognizable subgroup of diabetic patients. Yet clinically many of the elderly do progress to definite diabetes and may come to require substantial doses of insulin. We need some changes in the present laboratory criteria for diagnosis of diabetes in the aged in order to be able to recognize the disease in the predisease state. Beaser suggests that for persons who lack a positive family history of diabetes, glycosuria or an elevated blood glucose level, that the acceptable normal value at one or two hours of the oral glucose tolerance test should be increased by 10 mg. per cent at age fifty and an additional 10 mg. per cent at each subsequent decade.

Pregnancy represents a diabetogenic experience. Glucose tolerance tests decrease during the course of pregnancy, by whatever method it is measured except by the intravenous glucose tolerance test. If specific criteria of abnormality for the oral glucose test are employed then early diabetes in pregnancy can be detected. Starting with venous blood fasting glucose of 90, following as oral glucose load after one hour it is 165, 2 hours 145, 3 hours 125. Apparently the decreased glucose tolerance in pregnancy is due to a combination of reduced effectiveness of insulin and an increase in its catabolism. Normally the plasma insulin response to glucose is elevated during pregnancy and reverts to normal post-partum. However, the concomitant presence of a positive history of diabetes, a history of a large baby (nine to ten pounds) or a obstretrical history of perinatal or fetal death, or toxemia, then the diagnosis of diabetes is no longer in doubt.

Subjects with simple obesity do not have an increased incidence of frank diabetes on long term follow-up. However, obesity is present in a high proportion of diabetic patients and their weight reduction usually results in improvement of their glucose tolerance. Nevertheless, obese diabetics have a greater tendency to progression of their diabetes. Their plasma insulin response after a glucose load is abnormally elevated.

The paradox of the early diabetic usually obese with abnormal glucose tolerance tests and with a delayed but exaggerated response of plasma insulin is probably due to a pancreas reacting slowly and inappropriately to a glucose load. Actual depletion of pancreatic insulin reserve is suggested by the result of two studies. In one there was a decrease in plasma insulin concentration after three or more days of continued intravenous administration and in another a similar decrease in plasma insulin concentration after intraday glucose loading.

In acromegaly or other forms of overactivity of the anterior pituitary gland the serum insulin level is elevated even more than in early diabetes. A glucose load causes abnormal increase in plasma insulin levels, less after the oral than after the intravenous route. There is, however, considerable reversibility after successful therapy. The abnormal elevation of plasma insulin levels as in the obese diabetic, can lead to depletion and exhaustion of the pancreas with overt permanent diabetes if therapy is unsuccessful.

Patients with acute myocardial infarction show diminished glucose tolerance after the acute stage and this is independent of age. They show an abnormally elevated plasma insulin during glucose loading. Here again the oral glucose tolerance test is more likely to be abnormal and there is also a normal increase of plasma-free fatty acids during the tests. However, in one month to two years the tolerance test returns to normal except in those who had prediabetes which in time turned to overt diabetes.

In both cirrhosis of the liver and uremia the majority of patients showed an abnormal response to glucose loading, but the decreased carbohydrate tolerance is not associated with a decreased plasma insulin response. In uremia it is frequently reversible and is probably due to a decrease in hepatic glucogenesis.

Beaser points out that the available diagnostic tests for diabetes mellitus especially in conjunction with other clinical conditions still have many shortcomings and the presence of an abnormal oral glucose tolerance test is not sufficient in itself to conclude the existence of true diabetes. But with the aid of plasma insulin levels and accumulation of data from long term prospective studies the complicated problems of disturbed carbohydrate metabolism should in time be clarified.

L.H.N.

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Risks Associated With Vaccination Against Smallpox

Where smallpox vaccination is not adequately carried out, endemic foci of the disease persist especially in some areas of Asia, Africa and South America. From such foci one cannot avoid importation of smallpox into variola free countries such as ours. To date the United States has fortunately escaped re-introduction of the disease. The last documented case of smallpox was reported in 1949, but in 1962 a traveler on route from Brazil to Canada fell ill with overt smallpox within a day of arrival. He had stopped over briefly in New York.

Until the World Health Organization has achieved the worthy objective of smallpox eradication we must persist in employing all reasonable measures designed to maintain the current freedom of disease in this country. In other countries more than 63,000 cases were reported and many more are known to have occurred in 1965, in the endemic areas. Now that dexamethathiacarbazone is available for administration to known contacts it may be expected to reduce greatly the incidence of smallpox in many parts of the world.

Studies principally conducted in Europe of the complications and sequelae of vaccination have been cited as evidence for consideration of its abandonment or modification. However, the reports varied widely from country to country. It is understandable that as smallpox has disappeared in this country that a critical reappraisal of our attitude toward routine vaccination should arise on the part of some physicians and public health officials. It is known that a small but definite element of risk accompanies the widespread application of vaccination and re-vaccination. What is this element of risk and what measures can be employed to minimize that risk?

In our nation the assessment of the true risk associated with the procedures in vaccinating a patient were not truly realized until data became available from a national survey reported by Neff and his associates. They sought suspected complications that occurred during 1963 from a list of recipients of immune globulin and a national questionnaire of Pediatricians. The recipients of immune globulin represented a major source of information about the cases in Neff's study. Hyperimmune gamma globulin is prepared from blood of servicemen recently vaccinated and is the therapeutic agent of choice for dermal complications after smallpox vaccination. In this way Neff obtained detailed clinical data from five hundred and twenty nine of five hundred and fifty seven patients treated in 1963.

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Neff estimated that there were 6,239,000 primary vaccinations and 7,775,000 revaccinations performed during 1963. Over half were done in children under age five. They documented four hundred and thirty three patients with vaccine associated illness. Twelve had post vaccinal encephalitis all in the primary vaccination groups. Nine had vaccinia necrosum of whom six gave evidence of serious pre-existing disease. Most of the others suffered from a variety of skin lesions. Of the one hundred and thirty four who had generalized complications, fifty two were in children under one year old. There were one hundred and fifteen cases of accidental infections and this points up the need to clean off surplus vaccine from the site of vaccination.

Approximately two thirds of the complications that occurred were theoretically preventable if more careful screening for known contraindications to vaccination were practiced. The only real exceptions to this were post-vaccinal encephalitis and generalized vaccinia. Neff's data further suggest that primary vaccination should be delayed until after the first year of life, since infants under age one experienced the highest morbidity rates, 146.8 complications for one million.

The generally accepted contraindications to vaccination based on this and other[2] studies have now been incorporated in the recommendation of the Public Health Service Advisory Committee on Immunization Practices[3] for Smallpox. These are (1) eczema, a past history of eczema or eczema affecting a household member, (2) an active skin disorder of any type, (3) an antibody deficiency disease such as leukemia, lymphoma, Hodgkins, blood dyscrasia such as agammaglobulinemia, (4) treatment with immunosuppressive drugs or corticosteroids, (5) radiation therapy, (6) pregnancy, (7) infants under age one.

We are committed to preserve at the most acceptable cost the present freedom from the introduction of smallpox into this country and its spread among susceptible contacts. We now recognize that even among the rare problems reported as complications of vaccination against smallpox, a large portion of them are preventable. We adhere to the known contraindications to vaccination as presented by Neff and his associates above and the recommendations of the Public Health Advisory Committee on smallpox vaccination. In addition perhaps improved vaccines may become available as well as an antiviral agent that can act against the variola virus as penicillin does against drug sensitive organism.

L.H.N.

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Experiments In Medical Education:
1. Training A Family Physician

Few people doubt that it is becoming increasingly difficult to recruit present and future medical graduates to fill the dwindling ranks of the general practitioner. One reason is the dissatisfaction of medical graduates to enter a field in which the physician must necessarily have limited knowledge in a variety of fields in which he is called upon to practice, such as internal medicine, pediatrics, psychiatry, minor surgery, obstetrics, public health and others. Another reason is the harrassed life such a physician is forced to live with long hours and generally poorer compensation that specialists in medicine can command. In other words physicians are unwilling to enter a field in which they are threatened to become "second class" citizens.

No one, however, doubts the need of a special kind of physician, the family physician or first contact physician who will need to obtain mastery of various views and various treatments entailed in several specialized fields of medicine. Such an individual will also be required to have a comprehensive knowledge of the individual, his family, his social and psychiatric aspects so that he can significantly aid in the patient's overall progress and his associations with his surroundings. And so the problem really is how best to train a physician who is qualified to render comprehensive medical care to the American family.

One idea is a long term training of the family physician of the future, particularly for a period of two to three years following an internship. The training should have covered the fields of internal medicine, pediatrics, neuropsychiatry, some aspects of general surgery and orthopedics (minor surgery). This should be followed by certification to indicate that this has been accomplished. Obviously to accomplish this there would have to be established a department of comprehensive or family medicine in Medical Schools.

This means we are considering a new kind of family physician, one who has not heretofore been in existence and will require recruitment and very special training in medical institutions who have set up special departments for this purpose. The place of this type of family physician has heretofore been filled, in fact, by internists, pediatricians, psychiatrists, public health physicians as well as general practitioners. The reason for the multiplicity of physicians who are in fact playing the role of family physician is that basically all physicians could become general practitioners in the sense that they could advise regarding the general medical care of a particular family. However, it would be an inefficient way to achieve this aim.

The question, of course, is whether medical schools can meet the need for training for comprehensive medical care. It would, of course, require that the training of such a physician be as extensive and rigorous as that of other specialties. It would also require that the practice of medicine itself would be so structured that his role would be recognized. Specialization to be sure, does introduce its own problems but its growth is inevitable to the continued practice of medicine. It would also require that young medical graduates would be willing to enter such a field.

There is no reason why we cannot plan to train this new kind of generalist if we recognize the functions subserved by this new type of physician. First he must be able to care for the needs of the whole family, not an individual physician for each age group. He must be able to provide effective, personal and economical care and he must be specially trained for this role. He will be skilled in a body of knowledge of medicine, pediatrics, psychiatry, obstetrics, minor surgery and trauma. He will be trained to have a personal interest in people and not just their diseased organs. The common disorders are common but he must also be able to recognize the uncommon ones so that the patient can be referred to an appropriate specialist to furnish the necessary care. He will be highly proficient in the day to day problems encountered in practice.

Such a program requires the concept of the medical team where specialists serve as consultants and the family physician serves as the first contact physician assisted by a nurse, receptionist, laboratory technician, social worker, psychologist and other paramedical members. The family physician becomes the coordinator or team manager by providing the services that only he can provide and

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delegating those duties best done by others. This, in fact, is what many general practitioners, pediatricians and internists do now in a less structured and less economical way.

At McMasters University there will be such a program as an integral part of the educational program of the Faculty of Medicine, beginning July, 1967. It will consist of a Family Practice Unit staffed by full time family physicians who are faculty members in a department of Family Practice. It will be based at the Henderson General Hospital in Hamilton, Ontario. It is an experiment in medical education to train a family physician. It will, of course, be necessary to evaluate the venture carefully before any conclusions can be drawn. Obviously if the trained family physician becomes able to fill a satisfactory role in the medical team, it is possible that in the future more and more first contact care will be provided by the family physician and more specialists will come to assume consultant roles in practice and inevitably it might even lead to a decline in the practice of the specialists.

In the meanwhile two obvious consequences must follow. The present family physicians who accept these goals will perforce undertake to educate themselves and expand their knowledge in deficient areas such as growth, development, school and behavioral problems as well as efficient handling of common medical problems of the family.

The second consequence is that if family medicine is to become a new specialty then it must be centered on a clearly defined body of knowledge and be supported by well-conducted research. The research would deal with the family itself, the health needs of the family and various methods of providing health care. It is clear that many disciplines will be involved in such broad projects.

The speculations upon which the experiment at McMasters will be pursued will undoubtedly require further study and revision before family medicine becomes an established clinical discipline. We are still left with the question of how we are going to entice enough young men into the medical profession to become family physicians or primary physicians in this concept. There would be a minimum of four years after medical graduation before such individuals could come on the American scene. How many of these individuals would branch on the way into more concentrated efforts in the various specialties.

In essence there is a real need for such family physicians but their actual existence in adequate numbers to fulfill the real needs of the American population remains in doubt. In any event we will be looking to the experiment in McMasters with great interest because medicine is and must evolve new patterns to deepen its roots in science and broaden its scope of service to society.

L.H.N.

Infusion Thrombophlebitis

One of the most common diseases of medical progress is infusion thrombophlebitis. There has been increasing use of infusion therapy in hospital practice. The substances employed vary from glucose in water to glucose in saline to saline. Added frequently are vitamins, anesthetics and now antibiotics. As the infused solutions have become more varied and the duration of infusion prolonged, the incidence of infusion thrombophlebitis has also increased. The anesthetist inserts a needle in a vein and hardly a patient in intensive care is without an infusion. Post operatively practically every patient continues to receive infusion therapy for many hours or even days.

The incidence of infusion thrombophlebitis is so high that we have come to accept this complication uncritically as though it is necessary and not important. Nevertheless there is tenderness and redness of varying degree that can be seen near the vein on the first post infusion day. Later there develops a generally tender palpable thrombus at the site of infusion or in its immediate vicinity which can be readily observed by the physician and felt by the patient. Often the thrombosis and pain will begin at night giving the patient a sleepless, exhausting night. If a vein is cannulated in the mid forearm it may by thrombosis prevent infusion from many peripheral veins.

Since infusion thrombophlebitis and the tender thrombus which arises in consequence of it are so fairly common and can sometimes trouble the patient for months rendering a set of venous channels unusable for the future, the problem of infusion thrombophlebitis cannot be dismissed as clinically insignificant and more attention should be paid to prophylaxis as far as possible. Earlier studies to find predisposing factors in producing infusion thrombophlebitis have shown that long duration of infusion, acidity of the infusion fluid in long term infusions, the use of veins of small caliber, all increase the incidence of occlusion of the vein by clot. The studies with regards to the effects of infusion equipment, quality of needles, injection techniques and individual differences between patients have yielded highly conflicting results. But it is recognized that certain antibiotics such as Achromycin when added to infusion fluids are almost invariably followed by infusion thrombophlebitis.

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The discrepancies in results of studies conducted so far are probably the result of the difficulty in standardizing the experimental conditions, and especially to general endeavors to study too many variables in a single often small material. Elfving and his associates[1] first began their study of the problem of infusion thrombophlebitis in 1963 and the conditions of study were standardized as far as possible. With a sufficiently large material they concentrated on the duration of the infusion, the role of anesthetic agents infused and the role of individual factors in the genesis of infusion thrombophlebitis.

The study of 1,048 infusions showed clearly the great importance of the duration of the infusion and the acidity of the solution infused. If the infusion lasted two to eight hours the incidence of thrombophlebitis was 40 per cent but only 16 per cent of it lasted less than two hours. Glucose in saline, 10 per cent glucose or fructose did not materially alter the incidence. Some substances infused such as thiopental or barbiturates did not change the incidence of vein complication, but pethidine increased the incidence about one-third. Thrombophlebitis occurred less commonly in patients under age twenty. However, it was twice as common in women as in men but the existence of varices of the lower extremities or a history of previous thrombophlebitis did not increase incidence.

Earlier work have yielded contradictory results with regard to the significance of the pH. of the infusion fluid. Some found near neutralization of the infusion fluid lowers the incidence of infusion thrombophlebitis. Accordingly Elfving tested buffered and unbuffered fructose in 10 per cent solution. The unbuffered infusion caused 18 per cent complications. However, neutralization to a pH. of 6.8 reduced the incidence of complication to five per cent. When glucose solution was infused then buffering reduced the incidence of infusion thrombophlebitis from 20 to one per cent.

Heparin ointments have been favored by some for prophylaxis against infusion thrombophlebitis. Elfving found that it was possible to lower the incidence slightly and to mitigate the thrombophlebitis itself with this ointment. However, effective prophylaxis with ointment routinely is a cumbersome procedure as compared to a change of pH. of the solutions to be infused. The inconvenience to the patient caused by infusion can be most effectively eliminated and most practically by using buffered infusion fluids. Since starting routine buffering of infusion fluids Elfving and his associates have not encountered any deterimental side effects and have virtually eliminated infusion thrombophlebitis.

Inasmuch as the incidence of thrombophlebitis is very high after infusing certain antibiotics the next step it is hoped will be the development of an infusion fluid with antibiotics which will also reduce the painful and troublesome complication of infusion thrombophlebitis.

L.H.N.

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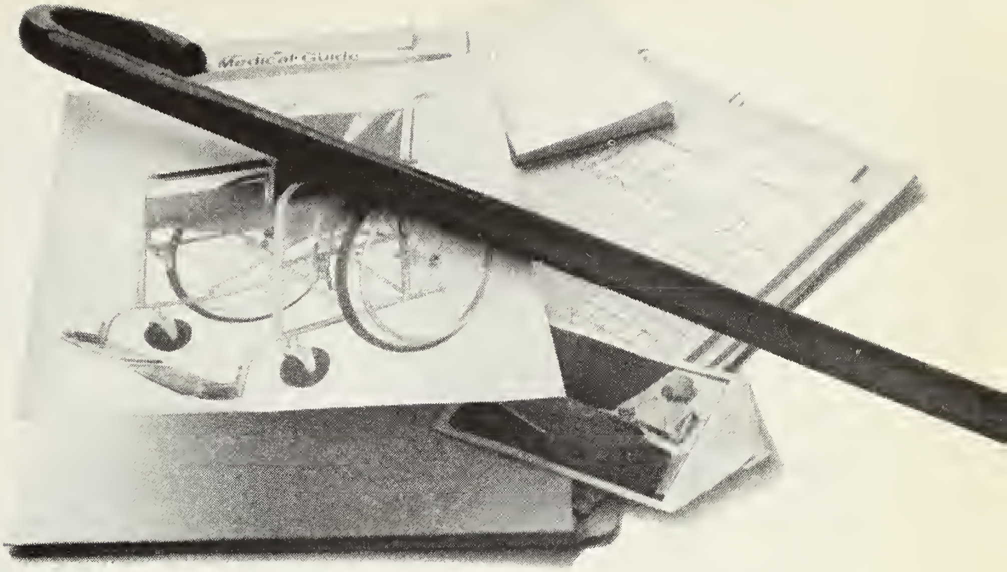
What Is "Informed Consent"?

Chayet[1] points out two important problems in which legal actions are brought against a physician. One of these is the claim of negligence or malpractice. In this type of case which is happily declining, the issue is whether or not the physician acted with less skill than another prudent physician would use who is practicing in the same or a similar community. In most cases of this kind the court would require evidence from another physician that the defendent did in fact practice below that standard of care.

Another type of case is one involving informed consent. When a physician proceeds without proper consent then the law terms his action "technical assault and battery." In actions of this kind there is no reference to what the community standard of care is. All that the patient needs to prove is that the procedure, whether biopsy, administration of a drug or operation performed, which led to some untoward consequence or injury, was performed without his consent. If he proves this he may be awarded damages for any injury suffered.

How does one obtain proper consent? This poses a very difficult medical-legal problem for the physician in almost every area of practice. Every operative procedure and many diagnostic procedures require the patients consent. The law appears to be quite clear on this point that the consent must be informed consent, that is consent freely given with a clear understanding of the relative risks and benefits of the procedure.

In most instances it is practically impossible to state the benefits and risks of a procedure in terms that would make a physicians task possible. For example a patient has carcinoma of the lung. He is slipping and we wish to give him chlorambucil. We can't tell the patient the probability of help nor the risk to his hematopoietic system. If we did we probably could never proceed with any of our therapy. Or we have a patient with heart fail-



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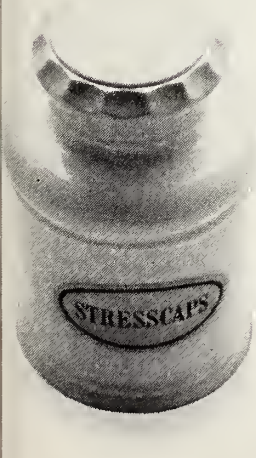

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ure who needs diuretics as well as digitalis. But diuretics can produce hypokalemia and irritable myocardium. They can cause hyperglycemia, precipitate gout and much else. Need we sit down with our patient and portray the risks and benefits. There came to mind innumerable instances in which we are obliged to try a new drug some of whose untoward consequences may not even be known for years.

The diseases of medical progress are many and increasing. Shall we explain to every patient his risk in receiving penicillin? Shall we explain that occasional rupture of the colon may follow a barium enema, that a liver biopsy may be followed by hemorrhage? There is little doubt that if we began to explain to a patient the known and unknown risks and benefits, practice of modern medicine would become too difficult. Shall a surgeon who is to perform a radical mastectomy tell the patient all the possible consequences of the mutilation? Shall we explain to a patient the possible risk of cerebral hemorrhage in the use of anticoagulants?

Several recent cases have raised again the perennial problem of consent. A Texas appellate court ruled that a man who had suffered a complete loss of hearing in his left ear as a result of stapedectomy was entitled to have his case reach the jury because the evidence raised a real question whether the physician had made a full disclosure of the risks and outcome probabilities of the operation.[2]

The patient testified that the physician told him that in cases such as his there was a 90 per cent chance of success. The other 10 per cent had neither improved nor worsened hearing. The doctor testified that he told the patient that in one per cent of cases hearing was entirely lost. The appellate court ordered a new trial to determine who was telling the truth. A written consent in which the risks were stated would have avoided the suit. Although a verbal consent is legally binding it is only so until the time comes to prove exactly what was said.

Patients often have remarkably poor memories and engage in a degree of fantasy once legal difficulties develop. The written consent obviously will have to be as specific as possible, listing the type of operation and the risks involved. A blanket consent may be even worse than a verbal consent. When a patient consents to anything and everything that may be done to him it may, Chayet[1] points out, have a definitely adverse effect on the jury.

A more difficult question raised by this case is the extent of the information that must be given to the patient before his consent will be considered truly informed in a court of law. It is on this point Chayet believes that the law will have to take into account the realities of medical practice. The law must understand the adverse psychologic effect on the patient were he to be informed of every possible risk attendant to even the simplest operation. The patient may even decide to endure "the lengthy list of horrors" given by the conscientious physician.

If we could apply the community standard to the consent cases as we do to the malpractice cases, it would be the most realistic way of determining how much information should be provided about risks and benefits by a prudent physician practicing in the same community under the same circumstances. In such an event the testimony of other physicians would be taken into account in determining whether the information was sufficient.

A recent Arizona case[3] has dealt with this question in a most enlightened manner. The case involved a cataract operation which the physician described as "very simple" with the further statement "there was no need to worry about it." The doctor testified that he did mention some of the risks just before the operation. It was quite clear, however, he did not list all possible risks, including the injury that did occur—a prolapse of the iris on each side of the incision. The Court stated "we refuse to hold as did the lower court that failure to disclose all reasonable and recognized risks inherent in an operation renders the consent ineffectual . . . the duty of the physician to disclose is determined by the normal practices of his profession in the particular community."

Of course there are other problems attendant upon the issue of consent. One is recognizing persons who are incompetent to give consent. Another—what is proper consent when one is engaging in clinical research and human experimentation.

If all courts like the Arizona Court will come to recognize and accept the medical realities of obtaining informed consent, then the doctrine of "technical assault and battery" will come to be applied with enlightened restraint.

L.H.N.

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Potentiation Of Coumarin Action By Phenylbutazone

We are aware of the drugs, like phenobarbital that interfere with coumarin action. The mechanism of its antagonism is based upon enzyme induction of glucuronides which combine with coumarins

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to render them ineffective. Now we have come to recognize other drugs like phenylbutazone which potentiates coumarin action. In fact the administration of phenylbutazone and oxyphenylbutazone to a patient already being treated with coumarin drugs can lead to serious hemorrhagic complications.[1]

Just how these drugs potentiate the prothrombinogenic effect of coumarins is not clear. It is not caused by impaired liver function or defective vitamin K metabolism since these drugs do not alter blood coagulation. Some have thought it was due to delayed renal excretion of the coumarins. Others have thought that they slow the disappearance of the coumarins from the plasma. Thus the idea arose that phenylbutazone inhibits activity of hepatic enzymes that metabolize the coumarins in the opposite mechanism of enzyme induction that phenobarbital generates.

Brodie[2] believed that phenylbutazone might displace the coumarins from their binding sites on plasma protein thereby making more free coumarin available at its site of action in the liver. Aggeler et al[3] have now reported evidence in support of this view. Their results show that phenylbutazone has a striking ability to displace warfarin from albumin in vitro and further that administration of phenylbutazone speeds up the disappearance of warfarin from plasma in man.

They tested three normal men and one fifty eight year old man with coronary heart disease. They took prothrombin times and samples of blood for warfarin content. Then they administered phenylbutazone 200 mg. twice daily. The prothrombin complex began to fall and within two weeks it had decreased to eight per cent of normal at which point bleeding from the bowel occurred. Vitamin K and transfusions restored the prothrombin time to normal.

The authors encountered a difficulty in testing plasma for phenylbutazone and warfarin because if they are measured by their optical densities, the similarity of these two is very close. They therefore developed another method of testing for these substances to eliminate this confusion. In each case they found that as the patients received phenylbutazone, there was a reduction in plasma levels of warfarin. This means that warfarin's disappearance rate was increased.

If potentiation of the warfarin effect by phenylbutazone was due to slowing or inhibition of the metabolism of warfarin, then the phenylbutazone administration should have raised the warfarin content of the plasma. In fact the concentration of warfarin in plasma dropped to half that which would be expected from the dosage of warfarin administered. It was only one-sixth the amount present when a comparable degree of hypoprothrombinemia was produced by warfarin in the absence of phenylbutazone.

When one drug causes increased rate of disappearance of another drug from the plasma, our first thought is that the first drug has induced an increase in drug metabolizing enzymes in the liver, a sort of enzyme induction. But if this were the explanation then the biologic action of the second drug should be diminished because free drug available at a specific site of biologic action is more rapidly depleted. This mechanism would cause interference rather than potentiation of action which occurred in Aggeler's patients.

An increased rate of disappearance of the second drug can also be produced when the first drug displaces the second from its binding to plasma protein. When this occurs, more of the second drug becomes available both to existing drug metabolizing enzymes and to specific sites of drug action in the liver. In this case even though the half life of the drug in the plasma is shorter, the biologic effect is greater. This is what apparently happenes when phenylbutazone potentiates the action of warfarin. By displacing warfarin from its binding sites on plasma albumin phenylbutazone has made increased quantities of free warfarin available both to drug metabolizing enzymes and to specific sites of biological action in the liver to produce hypoprothrombinemia.

The attempt to explain the antagonistic action of coumarin and phenobarbital offered an explanation of the difficulty of maintaining a therapeutic level of anticoagulants in such patients. It also led to utilizing the mechanism of enzyme induction in successful treatment of hyperbilirubinemic infants.[4] Perhaps the explanation of potentiation of coumarin action by phenylbutazone will also lead to new therapeutic approaches even as it has clarified for us the dangers inherent in treating patients with both phenylbutazone and coumarins.

L.H.N.

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Artificial Materials In Surgery: Autologous Tissue Materials

There are certain things in life for which there are no good substitutes.[1]

Great strides have been made towards improving host acceptance of homologous transplants. But on the basis of our present knowledge there is no good substitute for autologous tissue. Accordingly autologous tissues must be considered the standards against which all other types of procedures using protheses must be compared in terms of performance and permanence, especially when considering the various materials which can be used to effect arterial reconstruction. The perfect graft is "no graft," a close second is the arterial autograft. Endarterectomy is a form of using autologous tissue vascular material. Other types of material used for vascular reconstruction are autologous veins, the central tendon of the diaphragm and the pericardium and of course artificial fiber prostheses.

There is universal agreement that the arterial autograft represents the ideal type of vascular graft material. Even if the autograft is preserved by freezing under specific conditions, its implantation remains normally viable, the architecture remains intact, all the cellular and elastic tissue elements remain normal. Even when placed into a growing subject these implants exhibit normal maturation and growth.[1] The major disadvantage of the arterial autograft is lack of availability, since there are few arteries in the body that can be sacrificed for application in other regions. The autograft is further limited for use by the requirements of quantity, length, and diameter to effect extensive arterial reconstruction which are commonly performed today. The final problem is the serious question as to their usefulness in individuals who tend to have widespread atherosclerotic involvement of the arterial tree.

Endarterectomy which is theoretically preferable is good only in the case of short segment removal and the remaining wall is often not normal enough to allow for continued patency. One needs to produce an inner surface which is smooth and free of tags of tissue. The residual arterial wall in common with other segments of the arterial tree continues to show a propensity to develop obstructing atherosclerotic lesions and the endarterectomized segment itself tends to develop constricting fibrosis. Perhaps the tendency to fibrotic stricture at arteriotomy and endarterectomy sites is a manifestation of the fibrosing inflammatory element of atherosclerosis.

Many surgeons have therefore come to use a lateral patch which effectively widens the area of reconstruction and tends to minimize the effect of arteriotomy stricture and of the residual roughness of the segment. There is now a body of evidence which suggests that non-antologous patches may act as very short prostheses and be influenced only by the desirable "suture-line type" of healing as observed within one to two cm. of anastomosis of implanted prostheses. The issue will be settled when long term observation in humans of patch endarterectomy reconstruction become available.

The autologous vein also remains permanently viable with preservation of a largely normal mural architecture, although its wall undergoes medial thickening. Its expected longevity is far in excess of the arterial homograft, and therefore can be considered a permanently established material of arterial reconstruction. Of course autologous veins are subject to the same restrictions as autologous arteries, since there simply are not enough dispensable veins of sufficient length and diameter to satisfy the demands for arterial reconstructive materials.

For specific types of arterial reconstruction, such as closure of both atrial and ventricular septal defects and occasionally for widening the outflow tract of the right ventricle the central tendon of the diaphragm, rectus fascia and autologous pericardium have been employed. Although the use of non-vascular autologous tissue to effect arterial reconstruction may seem odd, in these specific regions non-vascular tissue may prove to be acceptable.

In time perhaps a prosthesis will be developed which will compare favorably with normal autologous aorta which is a near perfect graft. The ultimate challenge will be to develop a vascular prosthesis which can be implanted into a child and will grow apace with the attached host artery, and maintain a viable intact, stable and endothelialized inner fibrous capsule which will remain free of complications for the life of the individual.

At the present time grafting into the pulmonary artery and venous system is still in the experimental phase, because corrections are mostly in congenital defects and replacements must have a very long life. Perhaps the pericardium will be tried for use in the pulmonary artery. Small veins are very difficult to replace successfully and there is no successful infra-renal vena cava replacement or thoracic vena cava or portal venous system replacement.

There is still much to be learned even from the most acceptable graft fabrications. We know what the ideal properties of a vascular prosthesis should be. There should be absence of toxicity and allergenic properties. They should be durable and not deteriorate. They need to have the correct porosity and of course desirable handling properties. While dacron seems to be the best synthetic fiber at present for implantation, Wesolowski's work is directed towards importance of physical porosity and physical characteristics of synthetic

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vascular prostheses as determinants of their ultimate fate in healing.

Even though many patients are dramatically benefitted, vascular surgeons should not be complacent about their results but should attempt to recover all implanted prostheses, to analyze them in detail with a view of documenting all the complications which can occur, then applying this information to the development of better vascular prostheses.

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Thyroxin And The Organization Of The Nervous System

In the adult, one of the major functions of thyroxin is the regulation of temperature and of cellular metabolism. However in the newborn rat and for the first ten days of life thyroxin does not increase the metabolic rate (0_2 consumption) and yet thyroxin deficiency during this period has profound consequences for the subsequent life of the organism. The deficiency impairs learning ability and the development of the nervous system, and delays skeletal and somatic maturation.[1] Without accelerating metabolism what then are the influences upon the nervous system that are so vital.

Etkin[2] established the fundamental role of thyroxin in the maturation of the median-eminence area of the tadpole hypothalamus. This we must remember is a region of the brain which in higher animals controls many neuroendocrine regulatory mechanisms. One of these mechanisms, the secretion of ACTH in response to stress does not function during the early postnatal period. If thyroxin is added to an in vitro cerebellum from a newborn rat or mouse it accelerates myelogenesis. In the intact newborn rat during the first ten days thyroxin accelerates the deposition of brain cholesterol (which presumably represents myelinization) advances the age of eye-opening and increases spontaneous locomotor activity.

Schapiro and Norman have just published further work demonstrating that administration of thyroxin to the newborn rat will accelerate the maturation of the pituitary adrenal response to stress. It accelerates the development of the electroencephalogram and advances the age at which the rat will respond behaviorally and neurophysiologically to acute environmental stimuli. It will also increase the ability of the infant rat to learn a conditioned avoidance response.

The control rats five days old showed no change in adrenal gland content of corticosteroid after fifteen minutes of stress, but in thyroxin rats such an increase did occur. It would appear as if the thyroxin treatment advanced the age at which the stress they used, provoked the secretion of ACTH.

In the test for the maturation of the startle response, control animals exhibited no response in amount of activity to a sudden loud noise during the first nine to eleven post-natal days but at day twelve this stimulus elicited a measurable "startle response" and by fourteen days clear changes in activity occurred. In contrast thyroxin treated animals responded as early as nine days of age.

The infant rat brain before nine days of age has very little electrical activity and recognizable frequency patterns are not yet present. Even at day nine, wave patterns are not yet regular and distinct. However the thyroxin treated animals show a higher amplitude of activity at all age groups studied. At twelve days the experimental animals exhibited changes in both amplitude and frequency in response to a loud noise. Several days later (fourteen to fifteen) recognizable changes in the electroencephalogram occurred in the experimental animals in response to other external stimuli (cricket, light, keys). Their thyroxin appears to have accelerated the maturation of the central nervous system mechanisms underlying their physiological adaptive responses.

The ten day old rat's cortical nerve cells acquire properties of the mature neurone,[3] they sprout dendrites and axons and shortly thereafter rhythmic electrical activity is observed. In the absence of thyroxin the development of the central nervous system is severely retarded. Thyroxin therefore appears to play an important role for development of neurons during "critical" (or plastic) periods in early post-natal life. Such development establishes the web of interconnections that lay the foundation for later behavioral response of the organism. An important part in the development of these interconnections seems to be the myelinization of the fibers.

L.H.N.

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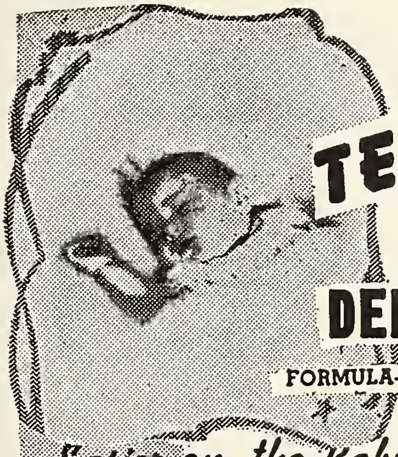

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Myxedema Heart Disease, Report Of One Case

Allen Chetrick, M.D.

■ Myxedema has been defined as a state in which there is essentially an absence of thyroid function. In this setting Zondek[1] in 1918 first recognized generalized dilatation of the heart of sometimes marked degree with sluggish heart action and depressed voltage of the electrocardiogram all of which reverted to near normal after the administration of thyroid. Thus the entity of myxedema heart disease was born. Fahr[2] in 1925 first described a case in this country and implied that congestive heart failure occurred secondary to myxedema heart disease. Willius and Haines,[3] and Christian,[4] however, doubted the existence of the entity of myxedema heart disease because they could not duplicate the dramatic shrinkage of heart size with thyroid treatment and because their cases of myxedema could not be disassociated from other organic cardiovascular disease states. This argument was partially resolved by the extensive case review of the heart in myxedema by Lerman, Clark and Means.[5] This study justified the establishment of this clinical syndrome with the reservation that the occurrence of associated congestive heart failure was rare. In other words cardiac enlargement may be a feature ascribable to myxedema alone but cardiac failure as an exclusive expression of myxedema heart disease is still controversial. The following case report is of interest because of the classical features of myxedema heart disease in a man with practically no subjective symptoms referable to either his myxedema state or to his heart.

This 37-year-old, white, single engineer was first seen on referral on June 4, 1964, because his company physical examination disclosed an enlarged heart on chest x-ray and low voltage on an electrocardiogram. There was no history of rheumatic fever, hypertension or congenital heart disease. He knew, however, that a chest x-ray in 1959*, at which time he was investigated for a suspected renal calculus, had demonstrated cardiac enlargement. There were no symptoms of respiratory insufficiency, chest pain, weakness or fatigue. Cold intolerance was not a problem, but his hands had been colder and his skin drier over the past five years. No history of chronic iodine or cobalt ingestion was obtained. His occupation did not expose him to any form of radiation. No thyroid disease was present in his family. His mother had late onset diabetes.

Physical examination disclosed a pale, expressionless male with obvious bilateral periorbital edema. The voice was deep and the skin dry and rough. The hands were "ice-cold." Hair and eyebrows were not scanty and the tongue was not enlarged. Lungs were totally clear. There was no cervical venous distention. The blood pressure was 114/96, the pulse 56 and regular, the temperature 98°F and the weight 183 pounds. The left border of cardiac dullness of the heart was 4.0 cm. beyond the left midclavicular line. The heart tones at the base of the heart were distant. No murmurs were present. There was no hepatomegaly nor ascites. The knee and ankle reflexes were definitely "hung-up." No peripheral edema was present.

The chest x-ray taken on May 27, 1964 showed marked generalized cardiac enlargement with a water-bottle configuration. The transverse cardiac diameter was 18.0 cm. while the transverse intrathoracic diameter was 30.6 cm. The lung fields were clear. The initial electrocardiogram showed depressed amplitude of all complexes. The T waves were abnormally flat or inverted in leads I, II, and V_{4-6}. A protein-bound iodine, obtained at a private laboratory, was 3.5 microgm. per 100 ml.

On June 14, 1964 he was admitted to the Yale-New Haven Hospital for further study. The white-cell count was 6,200 with a normal differential. The hemoglobin was 10.6 gm. and the hematocrit was 33 per cent. The blood indices were normal. The serum iron was 83 microgm. and the iron binding capacity was 280 microgm. per 100 ml. The urea nitrogen was 27 mg. per 100 ml. Serum electrolytes, calcium, phosphorous and liver function tests were all normal. Serum proteins and serum protein electrophoresis were normal. A protein-bound iodine was 0.4 microgm. per 100 ml. A triiodthyronine uptake study was in the hypothyroid range. A thyroid radio-iodine uptake was 3.0 per cent after two hours, 2.0 per cent after six hours and 2.8 per cent after twenty-four hours. A repeat thyroid radio-iodine uptake study was done after the administration of 10 units of TSH intramuscularly for four consecutive days. This showed an uptake o 3.2 per cent after two hours, 2.9 per cent after six hours and 2.0 per cent after twenty-four hours. The serum cholesterol was 406 mg., fatty acids 30.4 mg. and triglycerides 14.4 mg. per 100 ml. A morning serum cortisol was 23 microgm. per 100 ml. A twenty-four hour urine which measured 750 ml. revealed 7.59 mg. of 17-ketosteroids and 3.9 mg. of ketogenic steroids. A normal quantity of total gonadotropin by mouse uterine assay was present in a twenty-four hour urine.

Kymography demonstrated a reduction of cardiac amplitude in all regions of the heart. A carbon dioxide instillation study of the heart indicated an opaque density of 1.5

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* This chest x-ray was unobtainable, but a report concluded that there was generalized cardiomegaly and recommended investigation for congenital heart disease.

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to 2 cm. superior to the margins of the gas contained in the region of the right auricle compared to a normal of 5 to 7 mm. at this site. In addition a change in thickness was demonstrated when the patient shifted position. This study, therefore, was interpreted as demonstrating a pericardial effusion. He was discharged from the hospital on June 24, 1964. Two grains of dessicated thyroid daily was the only medication prescribed.

On August 24, 1964 at an office visit he offered no subjective changes other than the skin feeling less dry. Examination revealed the blood pressure to be 120/80, the pulse 80 and regular and the weight 171 pounds. The periorbital edema and facial pallor were gone. The heart tones were more audible. The relaxation phase of the lower extrmity reflexes were now quite brisk. An electrocardiogram showed a marked increase in amplitude of all complexes with normal upright T waves in leads I, II and all the precordial leads. A chest x-ray demonstrated a striking reduction in heart size and the heart was normal in configuration. The transverse cardiac diameter was now 13.4 cm. and the transverse intrathoracic diameter was 30.0 cm. The hematocrit had risen to 43 per cent, the protein-bound iodine to 4.8 microgm., while the urea nitrogen had fallen to 21 mg. per 100 ml. He has been followed periodically and was last examined on May 23, 1966 at which time he weighed 158 pounds. Whenever he was asked if he felt differently since the institution of thyroid, the answer was always in the negative. Yet his supervisor recently communicated with us and indignantly asked, "What had become of the easy-going man who once worked for him?"

The cardiac changes in myxedema heart disease are reported to occur only in extreme hypothyroidism. All parameters of thyroid function in our case demonstrated almost athyroidism. It is clear that the initial protein-bound iodine at a private laboratory was erroneous and inconsistent with the clinical picture. The failure of thyroid stimulating hormone to increase the radio-iodine uptake of the thyroid, the normal total gonadotropins in the urine and the normal serum cortisol level indicated a primary myxedema state. The low levels of 17-keto and ketogenic steroids were noted and unexplained save for the possibility that some of the urine was inadvertently discarded since the volume was only 750 ml.

The criteria for the diagnosis of myxedema heart disease as described by Zondek[1] were certainly met by this case. These included the marked cardiac enlargement with feeble heart action as seen by kymography and the electrocardiogram which showed the low voltage and characteristic T wave changes. Most convincing were the dramatic changes in the radiographic picture of the heart and the electrocardiogram which occurred two months after thyroid therapy was begun. In this interval the transverse cardiac diameter decreased 4.6 cm. and the electrocardiogram became completely normal. Furthermore no other type of heart disease was demonstrated.

Most authorities feel that the enlarged heart of myxedema represents a combination of cardiac dilatation and pericardial effusion.[6, 7, 8] The effusion has been in the past demonstrated by pericardial tap, yet aspiration did little to alter heart size. The carbon dioxide study indicated pericardial fluid in our case but it was elected to treat with thyroid alone since there was no evidence of cardiac tamponade. Nor was there evidence of congestive heart failure. Heart failure was manifested in 13 of 17 cases reported by Fahr.[9] Yet, as previously stated, Lerman et al[5] found this complication rarely present in myxedema heart disease. Gallagher[10] has attributed this infrequency of heart failure to the low level of activity of the myxedematous patient. Nevertheless our patient, who had documented cardiac enlargement for at least 5 years, had maintained a full schedule of activity without symptoms or signs of heart failure. It may be more reasonable to conclude that for overt cardiac decompensation to occur in myxedema, a concomitant cardiac disorder must also be present. Certainly in the older age group arteriosclerotic heart disease in a subclinical form may be difficult to recognize. It also follows that when an enlarged heart in myxedema fails to decrease in size after thyroid administration, hypertensive or coronary disease may be present.

Therapy in our case was initiated with 2 grains of thyroid daily despite a more cautious approach advocated by many to use small doses in order to avoid cardiac complications.[11, 12] This bold treatment was felt justified because of the relatively young age of our patient, the extreme hypothyroid state and the lack of evidence of the presence of any other heart disease. Close follow-up of his cardiovascular status was arranged as a precautionary measure and no complications of therapy were encountered. In addition to a weight loss of 25 pounds to date, thyroid alone corrected the anemia and normalized the urea nitrogen. The latter probably as a result of improved renal blood flow secondary to an increase in cardiac output. The fall in blood pressure from a hypertensive range has been previously reported[5] and may in part be due to a decrease in peripheral vascular resistance. In the face of all these physical improvements the only subjective change was a less dry skin, although a personality change was obviously seen at his place of employment. Even prior to therapy the paucity of symptoms of hypothyroidism was impressive and undoubtedly contributed to the delay of his diagnosis. This was probably the result of an amazing adaptation to a slowly developing myxedema state.

Summary

A case of myxedema heart disease is presented. The criteria for the diagnosis of this entity are discussed. The dramatic response to thyroid therapy is described. The unusual lack of symptoms of myxedema is noted.

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Critique And Cavil

The assemblage of contributions on hemophilia (JAMA 190:546-555 (Nov 9) 1964) merits comment since it directs attention to the great progress that has been made in reducing the hazards of surgical procedures in those unfortunate enough to have the disease. By way of contrast one might want to refer to some historical accounts of hemophilia in early America (*J Hist Med* 17:342-365, 1962; *Arch Intern Med* 110:144, 1962, *Blood* 19:243, 1962). It may be of interest to list here some of the surgical procedures that have been successfully carried out in hemophiliacs, as they have been reported in the literature: full-mouth dental extractions, vagotomy and gastrojejunostomy, Ramstedt operation for pyloric stenosis, subtotal gastrectomy, nephroureterectomy, prostatectomy, cholecystectomy and choledochostomy, excision of mandibular tumor, laminectomy, craniectomy, leg amputation through the knee, mid-thigh amputation, multiple tenotomies and fasciotomies in a patient, hip-joint exarticulation, appendectomy, intestinal resection, and mastoidectomy. There is a report of a hip disarticulation that was performed about a month before the case included in the above-mentioned assemblage. This report (*JAMA* 187:772 (March 7) 1964) was probably unknown to the author of the assemblage case when he labelled his as the second published report of hip disarticulation in a hemophiliac who survived the operation. Much of the reduction in operative mortality and morbidity can be attributed to improved surgical techniques and effective adjuvant therapy. AHF-rich plasma fraction is generally regarded to be a most potent therapeuetic weapon. Peanut extract, aminocaproic acid, corticosteroids, and flavonoids have been reported to be of value. No benefits from flavonoids have been reported (*JAMA* 181:41 (July 7) 1962).—George X. Trimble, M.D.

Prospectus For Medical Care—Twenty-first Century

E. Richard Weinerman, M.D.

■ The bicentennial of the Litchfield County Medical Association provides the occasion both for reassessment of the lessons of medical history and for anticipation of the continuous changes to be expected in the science and practice of medicine. If the life and work of the Connecticut practitioner in 1767 seem now to be charmingly antiquated, it is even more likely that the physician of 2167 will read our present reports and descriptions with almost total incredulity.

The past is, indeed, prelude—but the rate of change is anything but constant. As medicine advances it gathers momentum; the changes in the past two decades have overshadowed those of the previous two centuries. In the relatively short interval before the turn of this century, even more revolutionary changes are to be expected in the structure and content of medical care. It is the purpose of this brief essay to suggest the possible nature of the patterns to come in the next generation, with particular attention to the organization of medical care.

No projection of trends in medical care can possibly be valid apart from consideration of the changes in the society and the science which determine the role of the health services. The continuously evolving equilibrium between the two affects the characteristics of both healers and patients, the nature and distribution of disease, and the organizational structure within which the physician functions. The trend lines discernible today will be used as the basis for the interpolations which, hopefully can tell us something about medical care in the year 2000.

Underlying Assumptions

THE LARGER SOCIETY

Progress in health service as in any social effort, depends directly upon the underlying political, economic and cultural developments. In the healing arts, the relationship is particularly clear—and so oriented must be my basic assumptions for the future of medical care. These are, essentially optimistic: a world at peace and free from the harrowing threat of nuclear destruction; a political system in which equal opportunity for all citizens is an every-day reality; and a society dedicated through rational planning to the steady enhancement of the welfare of all its members. Such formulations are presented not so much a declaration of personal bias, but rather as a statement of the prerequisites for the progress which scientific and social advances now make possible in the field of medical care.

Further assumptions must be presented with respect to the influencing environment of medical care. The population will continue its demographic trends toward expansion and mobility. Urbanization will intensify, with ever greater interdependence between city and sustaining countryside. Mechanization and automation of the processes of production and distribution of goods and services will require a redefinition of the role of rational and skilled human beings. The economy will be recognized as capable of underwriting elimination of poverty (and, with it, caste distinctions), as it already has in theory with respect to ignorance. Perhaps then the next item on the agenda will be the total war against disease.

THE HYGIENE OF THE ENVIRONMENT

In a society so devoted to the well-being of its people, the practical task of control of environmental risks to health can be enthusiastically undertaken. Rapid mass transit systems will significantly diminish the present hazards of automobile traffic, air pollution and the blight of the inner city. The combination of scientific knowledge and social control will redeem the safety of water, air, food and those chemicals prepared for general use. An affluent society will have learned effective methods of regional cooperation in local government and public service—with planned community development, decent housing and recreational facilities, and esthetic surroundings for family life. Modern nutritional science will, at long last, replace faddism and profiteering as the basic influence in the eating habits of the population. Items for cigarette smoking will be preserved in museums as exhibits for those curious about the self-destructive foibles of their forebears.

Peace in the world will not have been achieved without removal of the now ominous threat of radiation contamination of the atmosphere. As a by-product of crucial importance to human welfare, the hazards of all non-military sources of radioactivity will also be recognized and essential controls invoked. In the same process, the needs of

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community will be accepted as of higher order than those of individual enterprise, making possible the effective containment of dangerous chemical and biological by-products of industry and agriculture. Perhaps most importantly, in view of the primary position of cardiovascular disease in the rank order of causes of death and disability, physical activity will be re-introduced into normal routine of the day.

THE MARCH OF MEDICAL SCIENCE

In few other areas of human endeavor is the phenomenon of an accelerating rate of change as evident as in the field of medical science. This is not the occasion for detailed projections of such theoretical and technical advances, but the general assumption must be clearly stated that the future organization of medical care will reflect in every aspect the explosion in medical knowledge and skill.

Prevention of diseases will be enhanced by steady progress in the development of vaccines and by further advances in the enhancement of biological defense mechanisms, particularly in relation to tumor-producing and respiratory disease viruses and to such intermediate organisms as the mycoplasma group. The twin bacterial menaces of streptococcus and staphylococcus will be contained by environmental controls and immunizing agents, with a similar vista for the persistent plagues of malaria, tuberculosis and venereal disease. Diseases now incurable, such as diabetes and rheumatoid arthritis, will become potentially preventable as research in genetic transmission and immune responses progresses.

Knowledge of preventive hygiene will be applied regularly at critical stages in the life process: infancy, school starting times, menarche, pre-marital, prenatal and post-partum periods, initially and periodically in relation to occupation, and at retirement. The principles of health maintenance, so clearly proven in relation to well child and maternity care, will be adapted for application to the other stages of life. New work in the understanding of nutritional adequacy in the preconceptual life period will enhance the biological quality of the newborn. Not the least important in this context will be that of voluntary family planning, freely available to all segments of society, based upon pharmacological control of the fertilization process.

Early detection of disease will remain the necessary basis of clinical therapy until that happy though still distant day when the known diseases are effectively prevented.

The approach to such early detection will be organized, periodic, applied to large population groups, and related to known exposure to risk in advance of the appearance of manifestations of active disease. The present techniques of multiple mass screening for "preclinical" stages of specified disorders—such as lung disease, diabetes and anemia—will be extended, automated, and applied with appropriate content to all segments of the population at the critical life points suggested above and to selected groups at and during the periods of exposure to special environmental risks. Specific laboratory screening measures will be available for ischemic vascular disease, essential hypertension, various forms of malignancy, renal and hepatic dysfunction, and certain mental disorders. The techniques of electronic graphing, radioactive scanning, cytological examination of body tissues and secretions, and automated biochemical analysis will be wedded to those of standardized recording of physical measurements—all programmed for processing and charting by the latest "generation" of computors, as aids to increased effectiveness in the early discovery of asymptomatic disease.

Dramatic advances will take place in the fields of *clinical diagnosis and therapy*. Refined diagnostic methods will be available with respect to the major groups of vascular and neoplastic disease. The results of laboratory, radiological and clinical case study will be digested, compared and analyzed electronically as the basis for the physicians' interpretation of causation, management needs and prognosis. Drug therapy will be reasonably effective for the control of many physiological aberrations—as in hypercholesterolemia, angina, hypertension and excessive autonomic nervous system activity. Electronic monitors will detect and mobilize the appropriate emergency measures in units designed for the intensive care of most life-threatening disorders. Basic victories will be won in the clinical management of hypersensitivity, oliguria and burns. Barriers to successful organ replacement will be overcome, radiant energy adapted to a wide variety of uses, effective control made possible in surgery with respect to hemostasis, hypoxia and shock.

The gains registered in the fields of *rehabilitation* will be spectacular. The application of rehabilitative principles and procedures will be an accepted part of the management of patients in early stages of active disease, as well as in the post-acute aftermath of disabling conditions. Understanding of the requirements of neuro-muscular retraining will lead to the restoration of effective function in a wide variety of disorders. Electronically operating prosthetic devices, often under micro-computer control, will closely simulate the function of the replaced body parts. Current leads in the improvement of impaired memory will enhance the mental function of older patients. In partnership with bio-engineers, vocational specialists, clinical psychologists and educators of many different kinds, the social and occupational restoration of disabled individuals will be widely extended.

Psychological and personal aspects of patient care will reflect the ferment now underway in our understanding of human perception, motivation and behavior—especially in the crucial early years of growth and maturation. Medical care will relate, in the first instance, to the person expressing the complex of dysfunction or disability, and to the pertinent aspects of his life setting—and only in such context to the specialized problems of the resulting pathology.

The unfolding knowledge of genetics will make possible the containment of certain transmissible and now incurable disorders, and will open exciting vistas for enhancement of the genetic code. High quality germ cell banks will bring new potentialities to the field of artificial insemination.

All such aspects of scientific progress will place new power and new responsibilities in the hands of both the health professions and society itself. Formidable problems of ethics and policy will require a re-examination of traditional codes—in the interests of the patient and the community as well as the health professions.

CHANGES IN THE PATTERN OF DISEASE

As a result of the many alterations in the social and physical environment, in the characteristics of the population, and in the effectiveness of medical care, significant change will also occur in the nature and distribution of disease. Differences in natality and mortality rates among various socio-economic segments of the population will narrow and disappear. The control of the more common pathogens will give rise to new and now exotic infectious diseases, bringing new responsibilities to future research scientists and clinicians. The extensive use of synthetic chemicals in food, clothing, cosmetics, pharmaceuticals, industrial processes and office and home appliances will produce more frequent sensitivity reactions. Advances in clinical medicine, newborn pediatrics and obstetrics will allow the survival and reproduction of an increased number of patients with familial and congenital disorders. The prolongation of life will continue to permit the development of chronic metabolic and neoplastic disease, despite the technical advances in early diagnosis and clinical treatment. New patterns of accident will be a concomitant of the changing order: exposure to radiant energy, supersonic speed phenomena, space abnormalities, and the like.

The most perplexing—and persistent—of the disease problems to be anticipated is that still unlabelled disorder of life which results from the fragmentation, frenzy, insecurity and alienation of the human condition in an increasingly mechanized and synthetic society. As urban and industrial "progress' continue both to liberate and to atomize the individual, disorders of social function will complicate those of degenerative physiological processes. A primary task of health service will thus be to promote, somehow, the integration of the person and the humanizing of his environment.

With changes in the setting, the subjects, the problems and the resources, the content of medical practice must and will be radically altered. It remains now to consider the inevitable changes to be anticipated in the structure of the medical care system itself.

The Organization Of Medical Care

Projections for year 2000 with respect to the organization and financing of medical care must, in the opinion of this writer, involve more in the way of evolution of presently discernible trends than wholly new forms and concepts. The prognostications presented here are based upon the assumptions of social and medical change stated above. The picture which emerges, it must be stressed, is one of prediction rather than personal preference.

GENERAL FORMULATIONS

Certain general statements may help to set the scene. The ascendency of those disorders which have in common the characteristics of multiple etiology, chronicity, and functional impairment will require the merging in practice of preventive, therapeutic and rehabilitative medicine. Of necessity, the social agencies now responsible for public health, clinical medicine, and extended care will operate in closely integrated fashion. The complexity of the biological and social sciences as they will continue to develop will require the team approach to health service, the joint use of sophisticated equipment in specially designed facilities, and the application of more efficient techniques of administration and financing. The maintenance of optimum levels of function and comfort, with or without the presence of continuing chronic disorders, will replace cure of acute disease or amelioration of active symptoms as the primary goal of the health professions.

In recognition of the central role of the family unit in the local community, basic health services will be family-centered and decentralized. The other side of this coin will be centralized facilities for those complicated special resources needed in support of the outlying basic services.

Finally, the principle will be accepted for medical care, as it has for education and sanitation, that basic policy control must be vested in the democratic and concerned community rather than in the professionals who provide the desired services. The latter, on the other hand, will retain control of professional and scientific arrangements and will continue to assume responsibility for the ultimate quality of the services rendered.

THE HEALTH SERVICE TEAM

The basis for effective medical care in any setting is *personalized, continuous and unified responsibility for the patient.* Ideally, this role should be played by a physician trained to provide such holistic service and motivated toward the protection of optimum function for the individual. Unfortunately, in light of trends discernible in 1966, few such physicians can be projected for the years past 2000—unless radical steps are taken now to modify the onrush toward sub-specialization and "technocracy" in medicine. If health-oriented physicians are trained to function in close liaison with other health personnel, personalized *medical* care of patients will persist and be strengthened in the year 2000. If not, new forms of primary care will emerge in answer to the undeniable need for a unifying agent in family health maintenance.

The core unit, at the family care level, will—in the expected latter case—contain a new type of health worker, representing a mixture of the functions of general practitioner, public health nurse, social worker and clinical assistant. This individual — yet to be properly named — will be specially trained in a two or three year course at the post-bachelor level and will function under medical supervision in the areas of health maintenance, preventive medicine, periodic screening, management of common and uncomplicated disorders, convalescent and extended care, and the like.

This *generic health worker* will be supported by broad-gauged internists and pediatricians, who will represent the link between hospital and health center and will be the source of referral to the various medical specialists in the more central echelons of service. Specially qualified public health nurses, social workers and rehabilitation therapists will complete the health team. Implicit in this projected pattern, of course, is the virtual disappearance of the general medical practitioner and the inclusion of internist and pediatrician among the ranks of referral and consulting specialists—a development already discernible in 1966.

Specialty practice will involve a growing majority of professionally trained physicians. They will be essentially hospital-based, working in support of the basic team in the community health unit and of the special personnel in affiliated long-term care facilities. New specialties will emerge in accordance with the advancing frontiers of medical science—in bio-engineering, tissue transplantation, and tumor chemotherapy, for example — while such established consultants as epidemiologists, biometricians, and psychiatrists will be more effectively utilized.

THE MEDICAL CARE FACILITY

The setting for family-oriented, local health service will be the *community health center,* staffed as indicated above by the basic health team, and provoding a continuum of protective health services including preventive care, primary treatment of disease, para-medical supportive services, and responsibility for arranging necessary medical specialist care. Such local health centers will be located in the residential and employment areas of the community, designed for the particular functions described, and flexibly planned for service to population groups of 10,000 to 20,000 individuals. These local facilities will relate administratively and functionally to the general hospitals and specialized medical institutions in the regionalized complexes described below. The community health center will serve as the base from which coordinated home care services will be provided to the chronically ill or incapacitated patients not in need of institutional supervision.

THE REGIONAL COMPLEX

Emerging naturally from the interdependence of these echelons of health service will be the consciously planned and jointly administered regional medical care complex. In each of the areas of the country characterized by a commonality of geography, communications, economic relationships, and medical service tradition, a formal affiliation program will involve at least one teaching medical center, a secondary orbit of general hospitals and affiliated specialty institutions, and a periphery of community health centers. Unified regional planning and management will permit efficiencies and economies of administration, a two-way flow of patient care services, and a coordinated system of training at all levels of professional and technical experience.

The Financing Of Medical Care

By the year 2000, the potentialities of the current methods of payment for medical care in the United States will have been thoroughly tested and compared with the experiences of other nations. Medical care benefits under the national social security system will have been extended to wider segments of the population and will have covered more of the spectrum of health service needs. Increasing public subsidy and regulation of voluntary prepayment plans will have established minimum standards and a certain uniformity of operation. Public welfare benefits will have been made available to most of the medically indigent in the population, while the requirements for federal appropriations will have minimized the differences among the various states. As a result, within the next decade, most of the population will be so involved with publicly supported medical care that a national financing system will emerge with minimum controversy as a logical method of coordination and efficiency.

The overall structure will be that of a nationally financed program based on a combination of social insurance and tax funds. Federal responsibilities, in addition to those of financing, will entail establishment of minimum standards, planning and evaluation of program, and support of training and construction aspects of the health service. Administrative and organizational authority will be delegated to the regional complexes, with appropriate flexibility and allowance for regional and local differences. The essential unit of service will be the community health center and the general hospital to which it is related. Health service personnel, including physicians, will be reimbursed on a flexible annual income basis, administered at the regional level, with strong representation of professional interests in the determination of reimbursement rates. Individual incomes will reflect peer group recommendations, considering quality of performance, assumption of responsibility, training and seniority. Prerequisites will include regular vacation, provision for sickness and disability, retirement benefits, professional insurance, and educational leave.

Medical care benefits under the national system will be comprehensive and free of co-insurance and deductible features. Medical audit, utilization review procedures, and other professional measures of quality control will reflect the importance given to the standards as well as the scope of the service benefits.

Implications Of These Trends

The trends toward effectiveness, complexity and expensiveness in medical care make inexorable the development of a highly structured future system of health service organization in this country. Powerful new tools will be placed at the disposal of the medical and allied professions, while — simultaneously—the changing nature of society will produce disease patterns not wholly responsive to purely medical therapies.

Such developments are interdependent and pose new and profound questions for society and its health workers. How can the needed rationalization of the medical care system be humanized, be kept flexible, be made supportive to the sick and the frightened? How can health service influence the re-synthesis of the individual in his family and community setting? What ethical precepts are needed to guide our use of the products of biological and technological research? How will the now-widening science-service gap be closed?

A wholly accurate forecast of the medical shape of things in the next century is impossible until such issues are resolved.

Summary And Conclusions

The major features of the system of medical care which have been projected for the 21st century can be anticipated as logical consequences of those changes in science and society which are clearly manifest in 1966 and which, in turn, have been engendered by the events in and around American medicine since the 1767 founding of the first local medical society. The evolution of our economy and political structure, the urbanization and mechanization of our society, the onrush of science and technology, the resulting changes in the patterns of health and disease among our people—all combine to alter the form and the structure of medical care.

As medical science becomes ever more complex and specialized, and as public demand for more and better health service becomes national policy and program, the pattern to be anticipated in the next century is possible of delineation. Its cardinal elements are those of the health service team in the *local* community health center, the coordinated network of medical care facilities in the *regional* complex, and the system of financing through social insurance and tax funds on the *national* level. Its major characteristics include the merging of preventive, curative and rehabilitative medicine, the emphasis upon family health maintenance, and the emergence of a new prototype of community health worker as a core element in the basic health team.

In 2167, as in 1967 and in 1767, the most significant advances in the health of the population will be made through control of the human environment, organized disease prevention, prompt treatment of active illness, and long-term support of chronic and disabling disorders. These goals, as always, will require the continuous partnership of science, community and medicine in the interest of the human welfare.

An Evaluation Of Intraperitoneal Sodium Cephalothin

Ira S. Goldenberg, M.D., A. Griswold Bevin, M.D., Andrew J. Graham, M.D.

■ The intraperitoneal use of antibacterial agents for prophylaxis and therapy has a relatively modern history with interest in this topic periodically renewed as new antibiotics are developed. The surgeon dealing with a normally contaminated gastrointestinal tract during an elective operation is keenly aware of the aftermath of spill of intestinal contents into the peritoneal cavity during operation. Techniques of performing closed gastrointestinal anastamoses were favored a few years ago to obviate this problem while somewhat later preoperative bowel preparation was developed for open anastamoses utilizing purgatives and/or poorly absorbed antibacterial agents. More recently, parenteral antibiotics have allowed the surgeon greater latitude and the possibility of contamination at operation is less feared than in the past. Nonetheless, in spite of careful preoperative preparation and surgical technique, contamination does occur during elective operations and may be the prelude to peritonitis or generalized sepsis. Even the biliary tract harboring local residual infection, especially when obstruction is present, may be the precursor of peritonitis after bile spill.

The risk of infection is obviously enhanced during emergency procedures following abdominal trauma or for diseases associated with peritoneal soiling such as appendicitis or diverticulitis. The latter are often accompanied by perforation of the bowel with local or generalized peritonitis which may precede a corrective operation by many hours or even days, while the developing systemic effects may increase markedly the operative risk in such emergency patients.

Initial interest in "sterilization" of the peritoneal cavity in patients with peritonitis developed in the early 1900's when sterile water lavage was introduced. Several years later, physiological saline was substituted and this method has remained popular to the present time since it acts mechanically to remove or dilute the effect of bacteria, bacterial toxins, chemical irritants and foreign material such as feces. In the 1940's reports were published extolling the efficacy of intraperitoneal sulfonamides for patients with perforated appendicitis and these prompted other investigators to evaluate many sulfa preparations in a wide variety of experimental and clinical situations. As the decade closed, however, the value of intraperitoneal sulfonamides was questioned and the popularity of this therapy waned. The development of antibiotics initiated a new era and it was logical that these should be used to combat peritonitis, but the intraperitoneal use of penicillin, streptomycin and the tetracyclines never became generally accepted. The saga of intraperitoneal neomycin is well known to all surgeons and is an excellent example of pharmaco-physiological detective work in demonstrating the potentiation of the drug as a neuromuscular blocking agent when used in conjunction with ether or d-tubocurarine chloride. In the most recent past, kanamycin has been advocated by many surgeons as the ideal agent for intraperitoneal application and has had widespread acceptance.

Utilization of powerful antibacterial agents to eliminate organisms locally is a most attractive thesis, but several criteria as outlined by Cohn[1] must be applied to such agents for use in the sensitive peritoneal cavity. The drug must be effective against a wide range of bacteria normal for the gastrointestinal tract as well as some of those less frequently encountered, e.g. *Clostridia* and, in addition, inflammatory reaction with the peritoneum must be minimal. If absorbed from the peritoneal cavity into the systemic circulation, an ideal preparation would produce no systemic reaction, although such absorption might be a dividend in itself by prolonging the drug effect against the organisms.

Materials And Methods

This is a report of the clinical use of intraperitoneal sodium cephalothin, a potent antibacterial drug prepared from the fungus, *Cephalosporium acremonium* which, like penicillin, acts to inhibit bacterial cell wall synthesis.[2] The spectrum of bacteria sensitive to cephalothin ranges widely and includes both gram-positive and gram-negative organ-

From the Department of Surgery, Yale University School of Medicine, New Haven, Conn. The sodium cephalothin (Keflin) used in this study was supplied by the Eli Lilly Company, Indianapolis, Ind.

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isms. *Pseudomonas* is uniformly resistant to cephalothin as are some enterococci. In animal studies, irritation of the peritoneum causing adhesions resulted from its use in powder form and also in solutions greater than 25% concentration. Cephalothin displays the interesting property of clearing from the serum of patients with renal failure by as yet undetermined mechanisms probably related to hepatic metabolism.

A total of 62 patients admitted to the University General Surgical Service of the Yale-New Haven Medical Center with a variety of intra-abdominal disease requiring 65 surgical procedures (elective and emergency) were evaluated. Inclusion of the patient was based on the actual or potential contamination of the peritoneum originating from the basic disease process or the organ to be resected. Patients were classified before operation according to overall clinical status as good, fair or poor. In emergency patients, this arbitrary status delineation was based primarily on evaluation of the degree of reaction to the peritoneal irritation present, and the other criteria of appraisal included physical examination of the abdomen and the degree of systemic response to the peritonitis as evidenced by temperature elevation, the level of leukocytosis with differential count, etc. In both emergency and elective patients, underlying acute or chronic dysfunction of cardiovascular, respiratory, renal or hepatic systems was also evaluated and contributed to the final preoperative status designation.

Many of the patients in fair or poor categories received parenteral antibiotics before, during or after operation and it was recognized that such therapy complicates evaluation of the intraperitoneal cephalothin. Exclusion of such patients, however, is impractical for a study of this type and, in addition, it was felt that precisely these very ill patients might benefit most from the intraperitoneal cephalothin.

Powdered sodium cephalothin was dissolved in 50 to 1500 cc. of 0.9% saline solution to make a final drug concentration of 0.3 to 4.0%. The major portion of a fresh preparation was instilled into the peritoneal cavity at the time of peritoneal closure and the remaining portion was used for lavage of the wound just prior to and during subcutaneous closure in many patients.

All patients were carefully evaluated postoperatively for the presence of possible infection as indicated by temperature elevation, level of leukocytes (including differential count), condition of the surgical wound and any evidence of local or systemic sepsis. In addition, many patients were evaluated for evidence of toxic or allergic reactions to the cephalothin by urinalysis and determination of blood urea nitrogen as well as liver function parameters, with comparison of these values to the preoperative determinations when available.

Information is incomplete regarding the spectrum of bacteria encountered during the operations performed. Suspect material was cultured in patients where purulence was found at operation, but for most elective operations, such data was not available.

The ultimate standard for evaluation of the intraperitoneal use of any preparation would reasonably be one of the degree of prevention of postoperative complications associated with bacterial infection, assuming no untoward systemic effects of the drug. Such an end point was utilized in the present study although, as mentioned above, it is recognized that coincidental parenteral antibiotic therapy could have affected patient response.

Results

The distribution of patients studied by the type of operation, use of parenteral antibiotics and postoperative complications is summarized in Table 1. Seven complications occurred which could be associated with infection. Three patients developed gram-negative septicemia: 1) a 68-year old woman, in fair preoperative condition recovered without residual problems following exploration of the common bile duct and performance of cholecystenterostomy for obstructing carcinoma of the ampulla of Vater; 2) a 69-year old man, in poor preoperative condition, succumbed to the septic problem following cecostomy performed for adhesion obstruction of the proximal colon; and 3) a 79-year old woman admitted with generalized peritonitis of 4 days' duration underwent emergency colostomy after the distal colon was found to be perforated at exploration and the preoperative septic course continued after operation. This patient died despite massive antibiotic therapy. The last 2 patients received antibiotics preoperatively. The surviving patient received no parenteral antibiotics postoperatively until the sepsis developed, while the patients who died were receiving antibiotics at the time the sepsis proved fatal.

Two additional patients developed wound infections after appendectomy both of whom had frank purulence at operation. Preoperative antibiotics had not been given but were administered to both of these patients postoperatively.

Minor wound infections developed in 2 patients who had colon procedures performed. The first was a 14-year old girl who had gunshot perforations of the colon followed by colectomy and colostomy who received antibiotics before, during and after operation. The second patient was a 66-year old female who while receiving parenteral antibiotics after abdominoperineal colon resection for carcinoma was noted to have a minimal wound infection.

Table I
Patient Summary

OPERATION		PREOPERATIVE CONDITION (NO. OF PTS.)			PREOPERATIVE ANTIBIOTICS (NO. OF PTS.)	POSTOPERATIVE ANTIBIOTICS (NO. OF PTS.)	COMPLICATIONS OF INFECTION (SEE TEXT ALSO)
		GOOD	FAIR	POOR			
COLON	Emergency[a]	0	5	5	3	7	Gram-negative sepsis—2 pts.
	Elective[b]	3	7	5	5	8	Wound infection—1 pt.
APPENDECTOMY		11	2	0	0	6	Wound infection—2 pts.
SMALL BOWEL	Emergency[c]	2	1	1	2	4	0
STOMACH-ESOPHAGUS	Emergency[d]	1	2	3	1	5	0
	Elective[e]	2	2	0	1	3	0
ABDOMINAL TRAUMA[f]		2	0	3	1	5	Wound infection—1 pt.
MISCELLANEOUS	Elective[g]	2	1	1	0	2	0
BILIARY	Emergency[h]	0	1	0	0	1	0
	Elective[i]	0	2	1	0	2	Gram-negative sepsis—1 pt.

[a] Colectomy, colostomy, ileocolostomy.
[b] Colectomy, colostomy, colostomy closure, ileocolostomy, polypectomy.
[c] Small bowel resection.
[d] Gastrectomy, plication perforated peptic ulcer, pyloroplasty-vagotomy.
[e] Esophageal reconstruction (colon), gastrectomy.
[f] Cholecystectomy, colectomy, colostomy, gastrectomy, splenectomy.
[g] Drainage subdiaphragmatic abscess, oophorectomy (abscess), ventral hernia repair.
[h] Cholecystostomy.
[i] Cholecystectomy, cholecystenterostomy, cholecystostomy.

Three patients had intraperitoneal instillation of cephalothin during successive operations and in this small group of patients it was possible to examine the peritoneum following the initial drug placement. There was no evidence of local inflammatory reaction or adhesion formation from the cephalothin.

No systemic toxic effects were noted after the cephalothin instillation in any patient. The leukocyte count, blood urea nitrogen and liver function parameters were not altered except as expected in association with the diverse disease processes present in many of these patients.

Comment

Forty-two of the 62 patients (68%) studied here were considered to be in fair or poor preoperative condition, while all of the patients presented a high potential for systemic or local infection. Seven problems of infection in such a group should be considered a low complication incidence. The therapeutic role of intraperitoneal cephalothin cannot be evaluated with precision since there is little doubt that parenteral administration of an antibiotic was very important to lack of infection in many of the patients evaluated. The study demonstrated, however, that intraperitoneal cephalothin is a safe and possibly effective therapeutic adjunct in patients with actual or potential peritonitis.

Summary

Sodium cephalothin solution was instilled into the peritoneal cavity in 62 patients at the conclusion of operations performed for a variety of diseases, all involving actual or potential peritoneal bacterial contamination. Only 7 patients developed postoperative problems associated with infection. No local or systemic effects were noted which could be defined as toxic reactions associated with the cephalothin.

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Torsion Of Fallopian Tube In An Adolescent Girl

Report of a Case

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■ Torsion of the fallopian tube is not an exceedingly rare condition. Since the first report of a case by Sutton[1] in 1890, followed by Delbet in 1892, there have appeared reports of many cases in which the torsion was due to various pathologic conditions of the adnexa.

Torsion of the undiseased fallopian tube is a much rarer occurrence. The first observation of torsion of normal adnexa in a virginal genital tract was reported by Stark in 1911 in a 46 year old virgin. Marked disagreement prevails among the authors as to the real frequency of torsion of an undiseased tube. Some believe that in most of the cases of twisted virginal tube the existing pathologic process was considered merely the result of torsion and strangulation.

In 1933, Regad[2] summarized his conclusion based on the 201 cases reported up to date. He revealed that torsion of the undiseased fallopian tube occurred in 24 per cent, torsion of the hydrosalpinx in 18 per cent, torsion of salpingitis and tubal pregnancy or twisted tumor in 13.5 per cent, torsion in course of pregnancy in 12 per cent, torsion associated with appendicitis or ovarian cyst in 9.5 per cent, torsion followed by spontaneous amputation in 5 per cent, and bilateral torsion in 4 per cent of cases.

Blum and Sayre[3] in 1937 reported a torsion of the tube in a 10½ year old girl who had not yet menstruated, and this was the fourth isolated torsion in a non-menstruating girl up to that date. (Hanson in 1922, Fiolle in 1927, and Block[4] in 1933.) The lack of connection with menstruation is an important point in considering the etiology and mechanism of such a torsion. In some cases it occurred shortly before or at the time of menstruation, perhaps it is due to venous congestion of the tubes.

Since 1937 there have been over 70 reports in the literature and a conservative estimate of the total number of cases of the isolated torsion of the tube which have been reported would be at least three hundred cases. However, very few cases of isolated torsion of the tube in non-menstruating virgins have been reported. Because of this rare occurrence the following case is reported:

Case Report

A fifteen year old white female was admitted to the Unity Hospital of Brooklyn, New York, on November 1, 1965 because of severe abdominal pain which started three days prior to admission. Pain was localized in the right lower quadrant, accompanied by vomiting and nausea on the first day of illness. The pain became more severe and radiated across the lower abdomen and then became generalized. There were no urological complaints.

Her family history was non-contributory. She had an appendectomy in 1960. Menarche had not yet occurred. Physical findings were limited to the abdomen and pelvis. The abdomen was generally tender, especially in the right lower quadrant. No rebound tenderness was elicited. No masses were palpable. Rectal examination revealed marked tenderness with a sense of fullness in the right adnexal region. Inspection of the vulva revealed a virginal introitus. Impression on admission was twisted right ovarian cyst.

Laboratory data: Hemoglobin 13.3 gm., hematocrit 39%, WBC 7,800 with 68 segments, and 24 lymphocytes. Sedimentation rate 37, VDRL—negative. A flat plate of the abdomen was negative for the presence of any masses. On the day of admission laparotomy was performed. Findings were as follows: Upon opening the abdomen there was about 500 cc. of serosanguinous fluid in the peritoneal cavity. The uterus was small, the left tube was grossly normal, the left ovary was small—1.5 cm. in length—was smooth and white. The right ovary was slightly enlarged with several follicular cysts. The proximal two thirds of the right tube was grossly normal. The terminal third measured 5 cm. x 3 cm., was grossly black, appeared gangrenous and was twisted 360° at its junction with the proximal portion of the tube. The omentum was lightly adherent to the terminal third of the tube which was lightly bound down to the base of the posterior leaf of the right broad ligament. The appendix was surgically absent. A right partial salpingectomy was performed and pathological report revealed hemorrhagic infarction of the fallopian tube with hematosalpinx. Culture of the peritoneal fluid revealed presence of E. coli. The postoperative course was marked by a moderate elevation of the temperature for four days. The patient responded well to antibiotic therapy and was discharged on the eighth postoperative day. She menstruated four weeks after the laparotomy was performed.

Summary

Torsion of the undiseased fallopian tube is infrequent and is very rare in the adolescent girl before menarche. A diagnosis of isolated tubal torsion is extremely difficult to make pre-operatively. Torsion of the fallopian tube should be included

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in the differential diagnosis of acute abdomen in the presence of adnexal mass in an adolescent girl.

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The Scientist as a Man

As to the scientist himself, the once-popular idea that he was either an absent-minded old gentleman or else a human reasoning machine has long since disappeared. The scientist of today is mostly a fairly ordinary chap, often a very human one, in all the meanings of that word. There is, in fact, little connection between scientific ability and wisdom, and scientific training has little effect in private life. The geologist, with his mind geared to a perspective of millions of years, may still be irritated by having to wait for five minutes for a bus; and the ethologist, deeply versed in the springs of behavior, may well be the victim of personal taboos and fetishes. The scientist, like everyone else, is to a large extent a puppet of his psychological and physiological makeup. He is essentially a man, not a machine, and as such is a prey to the ordinary human emotions of hope, fear, envy, ambition, and the rest which, unless he is careful, are apt to intrude into his assessment of himself and other people. In the last resort, there is no such thing as the disembodied, intellect and but few instances of the brain packed in ice. As Hoagland has well said, the human brain is a defensive and offensive organ, developed by evolution to promote survival in the same way as were claws and teeth. Certainly it did not develop for, and is quite unsuited to, the purpose for which scientists are supposed to use it—the objective pursuit of knowledge. It is thus understandable, for instance, that most research workers would prefer to make a discovery themselves, rather than that someone else should do so, though the identity of the human instrument is immaterial to the advancement of knowledge.—Parkes, A.S.: The Youngest Profession, *Perspect Biol Med* 10:59 (autumn) 1966.

Eli Ives Of New Haven And Yale

Gary C. Burget, B.A.

■ The custom for practicing medical men to give some measure of their time to university teaching is traditional in this part of the country. The tradition is a valuable one, for there is a unique inspiration—coming from his daily concern for the care of a large number of patients—that only the practicing physician can give to a medical student. This paper is offered as a brief and informal look into the life of one of Connecticut's earliest professor-practitioners.

Four men were appointed full professors to the Medical Institution of Yale College when it opened in the fall of 1813. They were Benjamin Silliman, Jonathan Knight, Nathan Smith—and Eneas Munson, a respected New Haven physician, who was then almost eighty years old. Munson's appointment as Professor of Materia Medica and Botany was intended for ornamentation only, since he declined the active duties of the professorship. These duties were performed by an Adjunct Professor of Materia Medica and Botany, a young New Haven doctor who for the next twelve years steadfastly did all the work of the professorship yet shared its glory with the aged Munson. This young physician was Eli Ives.

Eli Ives was born in 1778 into a family which was later to boast five generations of prominent New Haven physicians. His father was a doctor, a founder of the Connecticut Medical Society. After graduating from Yale College in 1799, Eli spent fifteen months as the Rector of Hopkins Grammar School in New Haven. During this period he began to study medicine both with his father and with his father's former teacher, Eneas Munson. He must have found Munson a stimulating teacher for in 1800 he shunned a glowing offer to become a tutor at Yale College and instead continued his medical education at what was then the most respected medical college in the country, the University of Pennsylvania. When, at the age of twenty-four, he returned to New Haven, he told his father that he wanted to set up a practice in some country town. His father's lucrative city practice was at its height and the older physician apparently saw certain disadvantages in small town medicine, so he urged Eli to go into business with him for at least three months, as an experiment, to see if the son could gain a foothold in New Haven. The experiment was evidently a success for "Young Dr. Ives," as he was then called, soon left his father to open his own office on the south side of Chapel Street across from Yale College. Here he acquired a practice which was so large that he found it necessary to keep three horses to keep up his business in the town and adjacent country; and that "in seasons of unusual sickness [he] hardly had time for the necessary sleep and meals."[1]

At this period the practice of medicine in New Haven was assuming for the first time a truly professional status. Educated medical men were uniting to better the standards of care and to protect themselves against the threat of charlatans, quacks and mountebanks. A colonial law of 1773 had prohibited the "practice of mountebanks in dealing out and administering physick and medicine of unknown composition indiscriminately to any persons whom they can by fair words induce to purchase and receive them"; yet unreputable doctors of all kinds still flourished, and were a constant threat to the educated physicians. In addition to this threat from the outside, there was considerable discord within the ranks of the regular doctors. Competition for patients was fierce. A physician called in consultation on a case would often use the situation unfairly to his advantage. Dr. Ives states, "It was not unusual at this period for such men as Drs. Elliot, Yale, Bird and Hurlburt when called upon to prescribe for a patient of another physician, on their first introduction, to sweep from the table into the fireplace all the medicines of his brother practitioner, and then like Paracelsus, magnify his own powers as supernatural."[2] It is not surprising, then, that thirteen reputable physicians of New Haven (including Eli Ives and his father) met in 1803 to form the New Haven Medical Association "to establish the practice of physic in this city on a respectable footing; to enable ourselves to live by the profession; to promote a good understanding and harmonious intercourse with each other, to avoid the disgraceful practice of undermining one another by doing business for a less compensation, and to exclude from our communion every person who shall obtrude himself amoung us without a regular introduction, and conforming to our established rules of practice."[3] A table was attached to this list of resolutions establishing fixed fees for various medical services. In

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addition, arrangements were made for care of the Almshouse poor. There was no regular hospital in the city until the founding of the New Haven Hospital in 1826. The Almshouse, "a plain building of considerable size, standing in a very healthful situation,"[4] probably had a small sick ward and served as a hospital for the destitute. A member of the New Haven Medical Association could contract with selectmen to attend the town poor. The city compensated physicians at rates equal to two-thirds of their normal fees: "two shillings for a day visit; four shillings for a night visit: one shilling for a puke; one do. for a purge; one do. for bleeding."[5] The New Haven Medical Association, by creating standards and rules of medical practice, unified educated physicians and set them apart from their less reputable fellows as a select group. It was in this newly established professional *milieu* that "Young Dr. Ives" worked to make his reputation as a practitioner.

As a physician Eli Ives rapidly gained the respect of his fellow doctors. After being in practice only four years he was elected a Fellow of the Connecticut Medical Society, became a member of its examining board and later—at the age of thirty-two—was elected secretary of the society. By the age of thirty-five his reputation was so solidly established that he was appointed associate professor at the new medical college of Yale. Henry Bronson, who was Professor of Materia Medica at Yale during the mid-Nineteenth Century, says of Ives' appointment: "It was then a great thing to be a professor. There were but four medical colleges in the country; these were in Philadelphia, New York, Boston and Hanover, New Hampshire; and the man who (on the ground of merit) was selected to give a course of public lectures, was considered high up on the professional ladder, if not at its topmost round."[6]

Eli Ives was associated with the medical school for forty-eight years during which time his interests ranged from botany and horticulture to the diseases of children. Throughout his lifetime he was an avid student of botany, and, indeed, knowledge of botany was an important adjunct to medical treatment in this period, since many remedies were made from plants cultured or collected locally. Ives knew the plants of Connecticut perhaps better than any man of his day and had, in fact, discovered several new species—including a species of *Asclepias* (milkweed) "found growing abundantly on the sandy plains east of Cedar Hill"[7] and a species of *Gnaphalium* (balsamweed), "first observed by me, in the company of Mr. C. Whitlow, . . . by the margin of a brook, a few rods north of Mr. Whitney's gun manufactory."[8] A perusal of Ives' students' notebooks—still preserved in the Yale Medical Historical Library—reveals that the doctor used his knowledge of botany to advantage in the treatment of disease. He recommended, among other things, slippery elm and sassafras for the treatment of thrush; arrowroot for erysipelas; juice of plantain leaves for the skin lesions of congenital syphilis and catnip tea and root of cattail flag for diarrhea. Most of these herbaceous remedies came from a botanical garden and hothouse which Ives kept on the grounds adjacent to the medical school. It was, in fact, remarked that the Professor "prescribed with a hoe from the resources of his wonderful botanical garden."[9]

—Yale University Art Gallery, Presented by the Medical Class of 1827.

Dr. Eli Ives. 1826.

Though Ives was a careful botanist, yet he was also a busy clinician. In this latter role he was so talented that Professor Bronson says "his knowledge was almost intuitive." His students apparently valued his teaching for their lecture notes are copious and meticulously kept. The following passages from the notebook of a Yale medical student of 1840 show that Ives' remarks on many subjects were highly accurate. Considering thrush, he remarks on predisposing factors.

> It is most violent in feeble, debilitated children. Hence it may be inferred that it is a disease of debility. It frequently follows other diseases in adults of robust constitution which have been debilitated by previous disease.[10]

In his lecture on "Sore Ears" he comments quite accurately on otitis media.

> Under this head I shall speak of purulent discharge from the cavity of the ears . . . If this discharge is stopped suddenly fever is frequently the consequence with full pulse—tense bowels and fulness of the Fontanelles.[11]

Speaking of worms he states that "All strong purges should be avoided in the case of Ascaris. . . ."[12] showing his awareness that strong irritants cause roundworms to migrate. In a great many instances, however, his conclusions about disease focussed too narrowly on the alimentary canal as the seat of derangement. For instance, he recommends cathartics for the treatment of "Infantile Erysipelas. The Rose of the West Indies."

> Pay little attention to the eruptions but let it be directed to the evacuation of the bowels. I have letters from Physicians who have followed my prescriptions—not treating the disease as a local one, but with cathartics testifying to the success of this practice.[13]

There are some portions of his students' notes which suggest that Ives was a master of differential diagnosis. One imagines that he recounted the following case with some measure of pride.

> Case of a woman in W. Haven who was supposed to be in the last stage of consumption. On re-examining the seat and cause of the disease I discovered that she was cutting the 4 *Dentes sapientiae*. After cutting the gums and giving some antispasmodics she recovered perfectly.[14]

His remarks on tongue-tie show good practical judgment.

> I have not seen a case where it was necessary to perform this operation. It is a very frequent notion among nurses that children are tongue-tied. Dr. Munson was called in one case to cut the frenum—he remonstrated, the nurse insisted—he then drew the back of his knife across the frenum with great success.[15]

Further evidence of Eli Ives' competence as a physician is found in his case reports. One of these appears in the first issue of the *Communications of the Medical Society of Connecticut* in 1810, a case of acute retroversion of the uterus in a pregnant woman occasioned by jumping from a horse.

> September 23, 1808, Mrs. A——, a woman of 40 years of age, . . . in jumping from a horse felt something give way in the pelvis; at this time she supposed herself to be about three months advanced in pregnancy. The shock was followed with great weakness, sensation of bearing down, . . . dysuria, nausea and vomitting, and all the train of *hysteric* symptoms, arising from the stomach sympathizing with an irritated and inflamed uterus.

Fifteen days later Dr. Ives examined the patient and it is obvious from the passage that follows that he gave scrupulous attention to details of physical examination.

> Entering the vagina, the finger met a tumor twice the size of a hen's egg, between the vagina and rectum. . . . A finger of the other hand was passed into the rectum, by which it appeared that the rectum was entirely obstructed by the fundus of the uterus, beyond which the finger could not pass . . . The uterus at the same time was felt by the finger in the vagina, wedged firmly between the sacrum and publis . . .

As is the case today, attempts at treatment often met with frustration.

> The patient was laid upon her back, her hips raised . . . exertions were made to restore the uterus, until her physicians were satisfied that it could not be restored in this manner. The patient was placed on her knees and elbows and repeated trials made to restore the uterus, but with no better success. . . . an instrument [was constructed] made of a cylinder the size of a finger, and eight or ten inches in length, on the end of which a head was formed, by winding flax and covering it with soft leather, as large as could be passed into the rectum. With this instrument oiled and introduced into the rectum, the patient on her knees, the thorax lower than the pelvis, two fingers in the vagina and much force applied by the instrument and fingers, the uterus was raised above the brim of the pelvis. The patient was enjoined rest and a recumbent posture; and after the usual period of gestation was delivered of a healthy child.

There is no doubt that Eli Ives was a clever practitioner, yet he was probably best remembered as a teacher. For forty years he lectured at Yale on Materia Medica, Botany, Diseases of Children and "Theory and Practice." Reverend Dutton (in Ives' funeral oration) estimates that he taught nearly fifteen hundred students. Henry Bronson attended lectures at the Medical Institution in the 1820's. Years later he wrote a vivid description of the Professor as he appeared then.

> Dr. Ives, then nearly fifty, . . . lectured on Materia Medica, Botany and Diseases of Children. He was tall and spare, of a weak organization, with a pleasant countenance and mild blue eyes, uncermonious and unpretending, familiar and agreeable in manners, and plain in dress. He had a high somewhat retreating forehead, which was heavily developed above and around the eyes, in the region of Gall's perceptive faculties. His appearance as he sat in his blue cloak with scarlet facing, reading his lecture from loose papers a little dingy with age, his voice rusty and feeble, his elocution hesitating and difficult, was not prepossessing. . . . At short intervals, unmindful of his notes, he would lean forward, rest his arms on the desk, and after a few preparatory hems, state a case, or relate an anecdote, in way of illustration of recreation. . . . His pleasantries were heralded by a certain twinkling of the eyes, and several extra hems which the mirth-loving of the class were quick to interpret. He was not a good storyteller, but his stories were piquant and amusing, and all enjoyed them, including the narrator. . . .
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> Notwithstanding his short-comings, Dr. Ives had many valuable qualities as an instructor and gave an excellent practical course. . . . He had treasured up in his capacious memory an immense store of facts gathered during many years of discriminating practice and thoughtful study, which he poured forth in unstinted measure.[16]

The notebooks of his students leave little question that the professor had a sense of humor. In his lecture entitled "Worms," he speaks of the treatment of tapeworm.

> For *Tenia solium* or *Cucurbitina* spirits of turpentine has been very successful; . . . A man of intemperate habits took a wine glass full of the spirits of turpentine. He said he never was so drunk in his life. A large tapeworm was evacuated.[17]

Concerning the treatment of toothache by extraction, he remarks, "It is known that the sight of the instruments will frequently stop the pain."[18] Elsewhere he tells of a woman who accidently set herself on fire and in her terror "ran down below where two elderly women were sitting who seeing her with her hair all burnt off and her clothes flaming they concluded they were come for and were excessively frightened."[19] And in his lecture on Flatulency he exclaims, "It is very mortifying to young ladies."[20]

Pastor Dutton states that since the time when Ives had looked at his Yale College catalogue and been dismayed at how many of his early friends had died drunkards, the doctor had been a firm believer in temperance. Yet, in his lecture on alcohol he remarks to his students, "It was very early used as a remedy and sanctioned by divine authority. Take a little for thy stomach's sake."[21]

Though Professor Ives' manner of teaching may have lacked polish, the substance of his lectures was considered good. The medical students of the Class of 1827, out of admiration for their teacher, commissioned a New Haven artist, Nathaniel Jocelyn, to paint the portrait which now hangs in the rotunda of the Yale Medical Library. One gathers from this painting that here was a wise, yet unpretentious man. It is known that he always wore a certain humility; his respect for Eneas Munson—"whose superior talents and continued friendship to me, I am happy on every occasion to acknowledge"[22]—seemed limitless. He appears, in the final estimation, to be a man who had little itnerest in fame, but sought and found fulfillment in his everyday pursuits: the practice and the teaching of medicine.

Notes

1. Henry Bronson, "Biographical Notice of Professor Eli Ives, M. D.," Republished from *The Proceedings of the Connecticut Medical Society,* (New Haven, 1867) p. 5.
2. Eli Ives, M. D., "Historical Sketch of the Medical Society of New Haven County," *Journal and Courier,* October 25, 1852.
3. Henry Bronson, "Medical History and Biography" from the *Papers of the New Haven Colony Historical Society, Vol. II,* p. 115.
4. *History of the City of New Haven to the Present Time,* ed. Edward A. Atwater, (New York, 1887) p. 89.
5. Bronson, "Medical History," p. 115.
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9. George Blumer, "Eli Ives—Practitioner, Teacher and Botanist," *The Yale Journal of Biology and Medicine,* vol. 4, no. 5, 1932.
10. Notes of an unknown Yale medical student, 1840, p. 5.
11. Ibid., p. 18.
12. Ibid., p. 37.
13. Ibid., p. 12.
14. Ibid., p. 47.
15. Blumer, p. 654. Also Ibid., pp. 66-67.
16. Bronson, "Biographical Notice," pp. 7-8.
17. Notes of an unknown student, 1840, p. 36.
18. Lecture notes of Anthony B. Burritt, 1830-31, p. 172.
19. Ibid., p. 149.
20. Ibid., p. 201.
21. Blumer, pp. 652-53.
22. Eli Ives, "Case of Uterine Polypus." *Communications of the Medical Society of Connecticut,* 1810, vol. 1, no. 1, p. 71.

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5. Dutton, Samuel W. S., D.D. "Address at the Funeral of Eli Ives, M. D., October 10, 1861." Republished from the *New Englander* for October, 1861. New Haven, 1861.
6. Ives, Eli, M.D. "Case of Retroverted Uterus," *Communications of the Medical Society of Connecticut,* I (1810), 78.
7. ———————. "A case of uterine polypus removed by ligature," *Communications of the Medical Society of Connecticut,* I, (1810), 70.
8. ———————. "Description of a New Species of *Asclepias.*" *American Journal of Science,* I (1819), 252.
9. ———————. "Description of a New Species of *Gnaphalium.*" *American Journal of Science,* I, (1819), 380.
10. ———————. "On the Comparative Quantity of Nutritious Matter which may be obtained from an Acre of Land when cultivated with Potatoes or Wheat." *American Journal of Science,* I, (1819), 297.
11. ———————. "On Spring Pasture." *American Journal of Science,* vol. 3, (1821), 355.
12. ———————. "Extracts from an Address Delivered by Professor Eli Ives Before the New Haven Horticultural Society at Their Annual Meeting in October, 1837." Published by the Society. New Haven, 1837.
13. ———————. "Historical Sketch of the Medical Society of New Haven County." By a member. *Journal and Courier,* October 22, 25, 26, 27, 1852.
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15. Notes of an unknown Yale medical student. 1840.

THE PRESIDENT'S PAGE

Politics! The General Assembly passed bills until two and three o'clock on its last several nights before finally adjourning—as required by law—at midnight on June 7th. When the cigar smoke had rolled away, some important health care legislation had been enacted.

Drug addicts are to be treated as patients rather than criminals. The Welfare Department's bill increased modestly the limits of eligibility for Title XIX benefits. One specific Health Care Center was authorized for the New Haven area. Although such centers and group practices may be beneficial, this heavily labor-sponsored project is not in the public interest, being a lay corporation contracting to supply medical care to selected groups—not needy individuals. It not only is tax free but may be subsidized for capital construction and cut-rate operation by public grants—i.e., taxes of its competitors and of the non-benefiting public. Diligent efforts by the Society, however, did restore some controls by the Commissioners of Health and of Insurance, made the professional staff responsible for medical decisions, and included some doctors—not more than 25%—on the Board of Directors.

The substitution of a medical examiner system for the coroner system was passed, subject to appropriation. The fee for external examination in medico-legal cases was raised. The pathologists will also probably be permitted to bill the coroner separately for autopsies according to their "usual and customary" charge. In cooperation with other states, air pollution control can be made more effective. The optometrists were prevented from making medical diagnoses of vision problems, but there again strong lobbying pushed through an authorization to choose from more than one profession in obtaining vision care.

The Society, in addition to its activity in these and other areas, had introduced three bills. The reporting of child abuse—immune from libel—will now include nurses, social workers and school personnel. S.B. 277 prohibiting state employees and officials from interfering with the practice of medicine and the rights of beneficiaries in Title XIX died in committee. But a tremendous education was obtained and a great battle won when our request for "usual and customary charges" under Title XIX was passed as an amendment to the law establishing uniform fee schedules for the healing arts professions. This will be a "pilot study" for one year starting March 1, 1968. A medical advisory committee with a majority nominated by the Connecticut State Medical Society will assist the Commissioner and will review questioned claims, though unresolved cases will be referred to the county associations before final recommendation. In March 1969, after review of the experiment, recommendation will be made to the General Assembly for extension of this method of payment, or its discontinuation, or its revision.

Obviously, all this wasn't just a "happening". Skipping for now the details of time and personal contact we might focus on one fact: we are on stage. In large measure it is our responsibility to make it work. Our argument was that a fee schedule would increase payments in some areas—an added burden on the taxpayer—and would be substandard elsewhere—diverting some patients from practitioners of their choice. However, if we are to prove our point and not make this method significantly more costly to the taxpayer than a fee schedule, we must all exercise restraint. And if there are "bad boys" among us who tend to degrade the image of the doctor, we must be firm with them. Should we fail to exercise internal and self discipline at this time, we can be assured, quite promptly, of much more rigid external controls.

E. Tremain Bradley, M.D.

FROM THE GENERAL MANAGER'S OFFICE

William R. Richards, m.d., *General Manager*
160 St. Ronan Street, New Haven, Conn.
Telephone 865 0587

Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

SUMMARY OF ACTIONS
COUNCIL MEETING
Wednesday May 17, 1967

Organization Of The Council For 1967-68

After opening remarks by President E. Tremain Bradley and introduction of the members of the Council, Stevens J. Martin, Hartford, was elected unanimously as Chairman of the Council for 1967-68. Dr. Martin then called the regular meeting to order.

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Bradley, Grendon, Polivy, Brandon, H. Caplan, M. Caplan, Fabro, Hess, Rogol, Abbot, Spitz, Shepard, Nolan, Jacobson, Cramer, Grant, Petrie, Pelz and Roch. Also present were Mrs. Lindquist, Mr. Villano and Dr. Richards. Absent were: Drs. Gardner, Egan, Hastings, Ayres, Wilson and Palomba.

II. Routine Business

Life Membership

It was VOTED to approve applications for Life Membership received from the following eligible Active Members:

Frank G. Amatruda, New Haven (NHCMA)
Charles W. Gaylord, Branford (NHCMA)

Election of Council Standing and Special Committees for 1967-68

Of special note is the deletion of several committees as follows: (a) Committee on Committees; (b) Liaison Committee on Medical Education and Hospitals; (c) Ad Hoc Committee to Study Paramedical Responsibility (*see below); (d) Committee on Medicare-Medicaid Experience (**see below); and (e) Committee to Implement Resolution on General Practice (***see below).

Donation to Connecticut Nutrition Council

It was VOTED to donate the sum of $200 to the Connecticut Nutrition Council as a contribution to the holding of a conference celebrating the CNC's twenty-fifth anniversary, May 18-19, 1967.

Date of Next Meeting

The next meeting of the Council will be held on Thursday, June 15, 1967, starting at 2:00 P.M.

III. Old, New and Special Business

Directives from House of Delegates, April 25, 1967

(a) *Resolution on: "Surgical Cases on Obstetrical Floors"*: It was VOTED to refer this resolution, adopted by the House of Delegates, to the Committee on Maternal Morbidity and Mortality for inclusion in its comprehensive study and "status" report on this subject which is under way, and to request the Committee to file a progress report on the subject in time for the next meeting of the Council.

(b) *Amendments to the Bylaws:* It was VOTED to request the staff to prepare suitable amendments to the bylaws to accomplish the following purposes (voted by the House of Delegates): (1) To delete the Committee on Publications; (2) To delete the Committee on AMA Education and Research Foundation; and (3) To change the name of the Advisory Committee to the State Commissioners of Welfare, Finance and Control to the "Liaison Committee with the State Commissioner of Welfare."

Report of Committee on Postgraduate Education on AMA "Millis Report"

It was VOTED to accept the report of this Committee on the "Millis Report," with commendation, and, with one minor change in the wording, to transmit the report to the Society's AMA Delegates and Alternate Delegates as the position on the Millis Report recommended by the Council, to be used for their guidance when the AMA House of Delegates received the Millis Report for action at its forthcoming June meeting in Atlantic City. It was further VOTED to request the staff to obtain copies of the Millis Report for distribution to all members of the Council.

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* It was VOTED to delete the Ad Hoc Committee to Study Paramedical Responsibility, and to transfer its members and assignment (to study the legal and ethical responsibilities of paramedical personnel performing medical services under the direction of doctors of medicine) to the Allied Medical Services Committee; also, to add members who are serving with pertinent Task Forces of the Regional Medical Program Study.

** It was VOTED to delete the Committee on Medicare-Medicaid Experience, and to transfer that Committee's duties to the Committee of Liaison Representatives with Connecticut General on Medicare B.

*** It was VOTED to delete the Committee to Implement Resolution on General Practice (House of Delegates, 4/64) and to request the Section on General Practice to study and make recommendations to the Council concerning futher implementation of this resolution.

1969 Annual Meeting

In light of the Council's recent action to eliminate conflicts with the Charter (i.e., the requirement that county meetings shall be held "at least 20 days" before CSMS annual meetings) by scheduling future annual meetings of the Society "on or about May 15," it was VOTED to direct the staff to negotiate with the Hartford-Hilton Hotel, Hartford, to reserve the dates of May 13-14-15 for the annual meeting in 1969. In 1968, it may be necessary to overlook the Charter's requirement in this regard, since the dates of April 30, May 1-2 have been confirmed and cannot be changed.

Special Ad Hoc Committee on Arrangements, 1968 Annual Meeting

Since the "local arrangements committee" of the county medical associations (furnished by the "host" county association) has not been utilized in recent years because Hartford has been the regular site for annual meetings and the staff, rather than HCMA, has been responsible for all arrangements, it was VOTED to appoint a special Ad Hoc Committee on Arrangements consisting of the President, chairman, the President-Elect and the Vice-President, to work cooperatively with the Committee on Program of the Scientific Assembly in evaluating and making recommendations concerning the format, associated functions, etc. of the annual meeting of the House of Delegates and the Scientific Assembly in 1968. It is understood that the work of the Ad Hoc Committee will be related to, but separate from, the work of the Program Committee.

Parliamentarian for Meetings of House of Delegates

It was VOTED that an Ad Hoc Committee be appointed by the President, who shall be chairman, to select a parliamentarian to assist the Speaker and Vice-Speaker at all meetings of the House of Delegates and to arrange with the person selected to be present at all such meetings. The members of the Ad Hoc Committee appointed by the President are: E. Tremain Bradley, Chairman; Kenneth F. Brandon; and Charles E. Jacobson.

COMPAC

(a) Drs. Bradley and Brandon reported briefly on the political symposium held by COMPAC on May 7 at the Hartford-Hilton Hotel, and also of plans to establish better lines of regular communication between the COMPAC Board of Directors and the Council. A summary of COMPAC activities during the past year was presented. Pursuant to these reports, it was VOTED to request the Chairman of the Council to appoint a committee to explore ways of establishing closer coordination between CSMS and COMPAC, and to make recommendations to the Council concerning same.

(b) It was VOTED to adopt a resolution concerning future educational grants to COMPAC, and Council recommendations for same, as follows:

RESOLVED: That the Council shall recommend all future educational grants to COMPAC at semi-annual meetings of the House of Delegates *only*, and shall recommend that such grants be included as identifiable items in the budgets for the fiscal years following, and be it further

RESOLVED: That the Council, before making any such recommendations in the future, shall have requested in writing from each of the component county medical associations the official attitude of each association's governing body and/or membership with respect to making such grants, and shall report its recommendation *and* a summary of these official (county association) attitudes to each semi-annual meeting of the House of Delegates at which such a recommendation is made.

Report—Representative to AMA Conference on Emergency Medical Services

It was VOTED to accept, with commendation, a report filed by J. Benton Egee, Newton, on the proceedings of this Conference, Chicago, April 6-7, 1967. By request of the Council, Dr. Egee attended the Conference as a representative of the Society. It was further VOTED that when the published proceedings of the Conference become available Dr. Egee be asked to revise his report in more narrative form and that copies of the revised report then be sent to each county medical association, each community hospital disaster preparedness committee, and the members of the CSMS Committee on Disaster Medical Care, for information and action, if indicated.

Report—Liaison Representatives with Connecticut General on Medicare B

Drs. Martin, Polivy, Cramer, Grendon and Richards reported briefly on the matters discussed at the last meeting of the liaison group held on May 15. Published minutes of the meeting will be submitted to the Council for study and acceptance on June 15. Pursuant to this report, and as a recommendation of the liaison group, it was VOTED to request the CSMS Liaison Representatives to plan and conduct an educational symposium on the problem areas of Medicare B, including utilization, the function of county review committees, etc., to which are to be invited as participants: members of the Council, county association officers, chairmen and members of county review committees, the CSMS Committee on Third Party Payments, and others interested and/or concerned with these matters. Hopefully, the symposium can be held within the next 4-6 weeks. It is understood that Connecticut General is willing to share the costs of the undertaking.

Resolution—Election of AMA Board of Trustees

It was VOTED to submit to the June meeting of the AMA House of Delegates the same resolution submitted to the Interim Meeting last Fall; i.e., "Rule for the Election of Members of AMA Board of Trustees." In brief, the resolution calls for the election of AMA Trustees on the basis of their running "at-large" rather than for specific seats on the Board, with the nominees receiving the most votes in relation to the number of seats open being declared elected.

Request—Committee on National Legislation

It was VOTED to approve a request of this Committee that up to $500 be allocated to its budget for the purpose of having a delegation of 4-5 members (selected by the Chairman of the Legislative Division) go to Washington, D. C. in late June to call on the six Representatives and two Senators from Connecticut. In addition to making an initial "legislative contact" with the Federal legislators, it is planned to discuss with them several pertinent measures now under study by Congressional committees which will ultimately be brought to the floors of the House and Senate for vote; i.e., amendments to Medicare, Medicaid, and Social Security cash benefits. The delegation is to file a report on the completion of its mission.

Resolution—Support of SB 1399, 90th Congress

Recommended by the Committee on National Legislation, it was VOTED to adopt and implement the following resolution:

WHEREAS: Thirty-four states, including Connecticut, have in force enabling legislation permitting groups of physicians to incorporate, and

WHEREAS: A number of such physician corporations, authorized under terms of these statutes, are currently operating in our state, and

WHEREAS: The expansion of group practice in the future is inevitable, and is worthy of legislative encouragement; and

WHEREAS: The practice of the U.S. Internal Revenue Service has nullified a principal advantage of medical corporations by refusing to approve the tax-sheltered pension plans of such medical corporations; therefore be it

RESOLVED: That the Council of the Connecticut State Medical Society direct its officers to help eliminate this arbitrary discrimination against physicians by actively supporting passage of S.B. 1399 (introduced by Senator George Smathers of Florida), which would require the U.S. Internal Revenue Service to treat professional service corporations and associations as corporations for federal income tax purposes; and be it further

RESOLVED: That a copy of this resolution be sent to the chairman of the Senate Finance Committee, and to the two Senators and six Representatives from Connecticut.

Abolishment—Committee on Relative Value Study

It was VOTED to abolish the Committee on Relative Value Study, and to transfer its operation and duties to the Committee on Third Party Payments. In the main, the "duties" will be to update the present Relative Value Schedule and to review the Schedule periodically with respect to changes in the unit values of procedures recommended by the various participating CSMS Sections and outside specialty groups.

Recommendation to Committee on State Blood Bank

In the face of reported shortages of fresh whole blood in the State, it was VOTED to request the Committee on State Blood Bank to study the possible use of frozen whole blood for transfusion purposes and to report its findings to the Council.

Recommendations—Annual Report of Committee on Disaster Medical Care

(a) It was VOTED to refer to the Committee on Hospitals, for study and recommendations for action, the following:

(1) That the medical staffs of the hospitals in the State of Connecticut be trained in the use of the Civil Defense Emergency Hospitals and be prepared to staff and use them as needed.

(2) That Connecticut hospitals be urged to establish inter-hospital radio communications systems in order to circumvent any communications failure in a natural or man-made disaster.

(b) It was VOTED to refer a third recommendation to the county medical associations, as information and for possible action, as follows:

That members of the Society be urged to participate, both as members of panels and in attendance as spectators, in any of the meetings that will be held throughout the State dealing with disaster medical care.

SB 1711—The Health Care Centers Plan

The Council was brought up to date on all legislative efforts that have been made in opposition to this measure, and was apprised that political pressures from its proponents are so strong that some form of the bill is almost certain to be passed by the General Assembly. It was VOTED to request the president, E. Tremain Bradley, and other CSMS officers to arrange a meeting with officials of Yale University and the Yale Medical School to ascertain what roles those institutions are playing with respect to SB 1711 now, and also what roles they will play if the measure is passed—particularly with respect to use of the multiple Federal grants which they have received to study "comprehensive medical care" in New Haven and in Connecticut.

Headquarters Building Security

Having been informed that the headquarters building had been burglarized twice within the past six months, with loss of typewriters and other business machines, it was VOTED to authorize the General Manager to have installed a suitable burglar alarm system at an initial cost of approximately $250 (materials, installation, etc.) and a maintenance and service charge of approximately $18 per month.

N.B. *The foregoing is a summary of the proceedings and actions of the Council on May 17, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT OPPORTUNITIES

PEDIATRICIAN — Pediatrician to associate with two established pediatricians in Southern Connecticut coastal town. Liberal salary first year, then partnership.

PHYSICIAN with background in internal medicine and/or pediatrics who is interested in a group practice in a rural town in Southern Connecticut. Hospital services available at several area hospitals.

G.P.—for association with another physician in a well-established practice in a growing industrial city in Southern Connecticut. Partnership possible after one year.

DIRECTOR OF PSYCHIATRIC TRAINING—Board certified. To direct 3-year approved psychiatric residency program at 2000 bed, community oriented, decentralized mental hospital. Also, to coordinate education for nurses, psychologists, social workers and occupational therapists in approved and university affiliated Programs. Previous teaching experience necessary. Starting salary range: $17,660-$19,850, excellent fringe benefits. All particulars should be sent in first letter, including references. Write: Superintendent, Connecticut Valley Hospital, P.O. Box 351, Middletown, Connecticut 06458.

PSYCHIATRIST needed for a community oriented mental hospital. To direct work in a 300 bed comprehensive mental health center, one of several units in a 2000 bed state mental hospital. Opportunity for teaching, clinical work and research. To work with a team of social workers, psychiatric residents, psychologists, occupational therapists and nursing staff. OPD, day-care, inpatient consultation and emergency care are available. Opportunity for association with Wesleyan University, Yale University and UConn. Starting salary: $14,240 to $18,220, annual pay increases. Excellent fringe benefits. All particulars and references in first letter. Write: Mehadin K. Arafeh, Superintendent, Connecticut Valley Hospital, P. O. Box 351, Middletown, Connecticut 06458.

OCCUPATIONAL PHYSICIAN to associate with 2 other physicians and a staff of 9 nurses, 2 safety engineers, 1 X-ray laboratory technician, part-time optician and clerical staff in a modern, fully equipped Occupational Medical Department in Central Connecticut. Duties of Occupational Physician involve a program of prevention and treatment of occupational injuries, illnesses and a continuous program of employee health evaluation beginning with job preplacement examination. Emphasis is placed on medical evaluation of the employee with particular reference to physical demands and environmental exposures of his individual job, and participation in employee health counseling, periodic examination programs and evaluation of environmental exposure factors for employee health and safety.

A program of indoctrination will be conducted for the new physician. Work schedule consists of 5 days a week and no obligation to be on call nights or weekends. Outside practice permitted if it does not interfere with regular duties, and he will enjoy an excellent relationship with local practitioners, consultants and hospitals in the Hartford-Springfield areas. Salary commensurate with individual's experience. Write or call: 623-1621. Dr. Lawrence Coleman, Hamilton Standard, Bradley Field Road, Windsor Locks, Connecticut 06096.

MEDICAL DIRECTOR—a leading industrial firm needs a top man, Board qualified in internal medicine or occupational health. Will deal with various industrial health problems and supervise a staff. Responsible for planning and implementing new programs. Most likely will have clinical or industrial experience. This man may come from a university, hospital research group, private practice of internal medicine or government projects. Headquarters, New England, Top company, top conditions. Salary to $35,000. All fees paid by company. Contact: Richard P. Rita Personnel, 993 Farmington Avenue, West Hartford, 236-3249, with resume.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

1968 MEETINGS

April 30, May 1-2 —— 176th Annual Meeting of Connecticut State Medical Society to be held at Hartford-Hilton Hotel, Hartford, Connecticut.

Welcome, New Members . . .

Fairfield County Medical Association

Willet R. Bowen, M.D.—Route 7, Brookfield, Connecticut 06804

Francis J. Browne, M.D.—1425 Bedford Street, Stamford, Connecticut 06905

Harold S. Cole, M.D.—Dept. of Pediatrics, N. Y. Medical College, 106th Street & 5th Avenue, New York, New York 10029

Gerald E. Cooney, M.D.—2685 Main Street, Bridgeport, Connecticut 06606

Saul Feierstein, M.D.—1603 Summer Street, Stamford, Connecticut 06905

Charles H. Gray, M.D.—4 Cove Ridge Lane, Old Greenwich, Connecticut 06870

Richard B. Knapp, M.D.—Stanwich Road, Greenwich, Connecticut 06830

Paul C. Mastrony, M.D. — 2156 Park Avenue, Bridgeport, Connecticut 06604

Peter J. McLoughlin, M.D. — 1984 Park Avenue, Bridgeport, Connecticut 06604

Robert D. Osborn, M.D.—153 East Avenue, Norwalk, Connecticut 06851

Gerald D. Roberts, M.D. — Hall-Brooke Hospital, Westport, Connecticut 06880

Francis P. Saunders, M.D.—85 Osborne Street, Dan-Bury, Connecticut 06810

Charles G. Silberman, M.D.—47 Long Lots Avenue, Westport, Connecticut 06880

Karl C. Suerig, M.D.—49 Lake Avenue, Greenwich, Connecticut 06830

Virginia Suttenfield, M.D.—500 Wire Mill Road, Stamford, Connecticut 06903

Ahmed Usman, M.D.—21 Broad Street, Stamford, Connecticut 06901

Norman R. Vincent, M.D.—10 Washington Avenue, Bridgeport, Connecticut 06604

Cyril Waynik, M.D.—881 Lafayette Street, Bridgeport, Connecticut 06603

Litchfield County Medical Association

Samuel D. Danzig, M.D.—66 Bridge Street, New Milford, Connecticut 06776

Robert W. Harkins, M.D.—Judson Road, Woodbury, Connecticut 06998

Stuart Ragland, Jr., M.D.—Smith Hill Road, Colebrook, Connecticut 06021

John D. Sproul, M.D. — New Preston Hill Road, New Preston, Connecticut 06777

Ronald G. Zeffiro, M.D.—Litchfield County Hospital, Winsted, Connecticut 06098

New London County Medical Association

Ralph C. Andrews, M.D.—Medical Art Building, Gales Ferry, Connecticut

Richard M. Barry, M.D. — Sandy Hollow Road, Mystic, Connecticut 06355

Robert Kerrigan, M.D.—87 Lafayette Street, Norwich, Connecticut 06360

William F. McKeon, M.D. — 57 Lafayette Street, Norwich, Connecticut 06360

Peter I. Rabinovitch, M.D.—175 Boton Post Road, Waterford, Connecticut 06385

Hartford County Medical Association

Kenneth F. Bean, M.D.—708 Farmington Avenue, Bristol, Connecticut 06011

Charles W. Boren, M.D.—200 Retreat Avenue, Hartford, Connecticut 06103

Ian R. Cameron, M.D.—200 Retreat Avenue, Hartford, Connecticut 06103

Mary S. Coley, M.D.—Newington Hospital for Crippled Children, Newington, Connecticut 06111

Mary T. Cullen, M.D.—27 Fernwood Road, West Hartford, Connecticut 06119

Richard J. Fauliso, M.D.—111 Gillett Street, Hartford, Connecticut 06105

Bernard C. Glueck, M.D.—400 Washington Street, Hartford, Connecticut 06102

Grant R. Golub, M.D.—85 Jefferson Street, Hartford, Connecticut 06103

Robert E. Hicks, M.D.—233 Main Street, New Britain, Connecticut 06051

Jorge Leicach, M.D.—73 Cedar Street, New Britain, Connecticut 06052

James E. O'Brien, M.D. — 114 Woodland Street, Hartford, Connecticut 06105

Joan M. Platt, M.D.—85 Jefferson Street, Hartford, Connecticut 06103

Eugene L. Quinto, M.D.—283 Main Street, New Britain, Connecticut 06051

Jay E. Selcow, M.D.—85 Jefferson Street, Hartford, Connecticut 06103

Robert M. Sullivan, M.D.—477 Connecticut Boulevard, East Hartford, Connecticut 06108

John W. Visnauskas, M.D.—83 Vine Street, New Britain, Connecticut 06052

Middlesex County Medical Association

Alan E. Bernstein, M.D.—120 Washington Street, Middletown, Connecticut 06457

Harry Y. Twiss, M.D.—Connecticut Valley Hospital, Middletown, Connecticut 06457

James Kar-Kee Yue, M.D.—725 South Main Street, Middletown, Connecticut 06457

Windham County Medical Association

Thorburn S. McGowan, M.D.—University of Connecticut Infirmary, Box U-11, Storrs, Connecticut 06268

General Principles of Hospital - Medical Staff Relationships

Approved by

The Connecticut State Medical Society—February 16, 1967

and

The Connecticut Hospital Association—May 1, 1967

The following "General Principles" were developed jointly by the Society's Committee on Hospitals and the Council on Professional Practices of the Connecticut Hospital Association. Approved subsequently by the Council of the CSMS and the Board of Trustees of the CHA, and mailed directly to administrators, presidents of boards of governors, and presidents of medical staffs of all hospitals in the State, the "Principles" are published herewith for the information of members of the Society.

A major purpose of hospitals and physicians is the provision of the best possible medical care to patients. To fulfill this purpose, full cooperation among medical staff, governing boards and administrative heads of hospitals is required. A mechanism is needed that will bring these partners in hospital endeavor into frequent and close contact. It is necessary to establish an organization that will provide adequate and effective channels of communication and a clear understanding of the role of each group.

The Connecticut State Medical Society published its recommendations concerning improved liaison between hospital medical staffs and boards of trustees in March, 1963. In December, 1964, the AMA House of Delegates adopted "General Principles of Medical Staff Organization." The Board of Trustees of the AHA approved a "Statement of General Principles of Medical Staff Organization" in February, 1965. The Joint Commission on Accreditation of Hospitals has published model medical staff bylaws and other statements concerning hospital and medical staff organization. The following ten principles are based on these prior statements as a guide for physicians and hospitals in Connecticut.

A. Communications:

1. A Joint Conference Committee has proven to be the most effective mechanism to ensure open communication between the board, the administrator and the medical staff. While it is not responsible for making decisions, it should encourage candid and free discussions.

2. Attendance by members of the medical staff, who may be elected or appointed, at meetings of the governing board can be advantageous. There should also be such representation at appropriate administrative committees (e.g. Management Committee, School of Nursing Committee).

3. The administrator, or designate, should attend medical staff committees, particularly those that affect the operation of the hospital (e.g. executive, therapeutics and operating room committees).

4. The administrator should establish and maintain free and open communication with individual members of the medical staff on a personal basis and with due consideration for the more formal channels of communication outlined above. Such personal contact can be an effective means for promoting understanding between the administrator and members of the medical staff.

B. Basic Principles of Organization:

1. The administrator is the chief executive officer selected by the governing board to carry out its policies. He has the responsibility of efficiently coordinating the activities of all departments and services of the hospital.

2. Responsibility for the quality of medical care is delegated by the governing board to the medical staff and this responsibility can be effectively carried out through a medical staff executive committee (or other appropriate body) which is recognized as the authoritative body of the medical staff.

3. The medical staff executive committee should consist of chiefs of major clinical departments who may be either elected or appointed. The governing board, after due consultation with the medical staff, may initiate and should ratify the selection of the chief of a clinical department, whether elected or appointed, because the governing board delegates to him the authority necessary to fulfill the responsibilities of the office. It may also contain other elected officers or members of the medical staff.

4. All applications, appointments and reappointments to the medical staff should receive final action by the governing board taking into account the recommendations of the appropriate body of the medical staff. Appointments and reappointments should clearly delineate the scope of privileges being granted and should be reviewed annually.

5. While appointment to the medical staff is a privilege, it should not be terminated or restricted

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(oxazepam) Wyeth

When prescribing, carefully observe dosage recommendations and appropriate precautions, especially as pertaining to the elderly (see Wyeth literature or PDR as well as "IN BRIEF" below).

IN BRIEF.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

Precautions: Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. Withdrawal symptoms upon discontinuation have been noted in some patients exhibiting drug dependence through chronic overdose. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive, prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Withdrawal symptoms following abrupt discontinuance are similar to those seen with barbiturates. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 6 years; absolute dosage for 6- to 12-year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leucopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever and euphoria.

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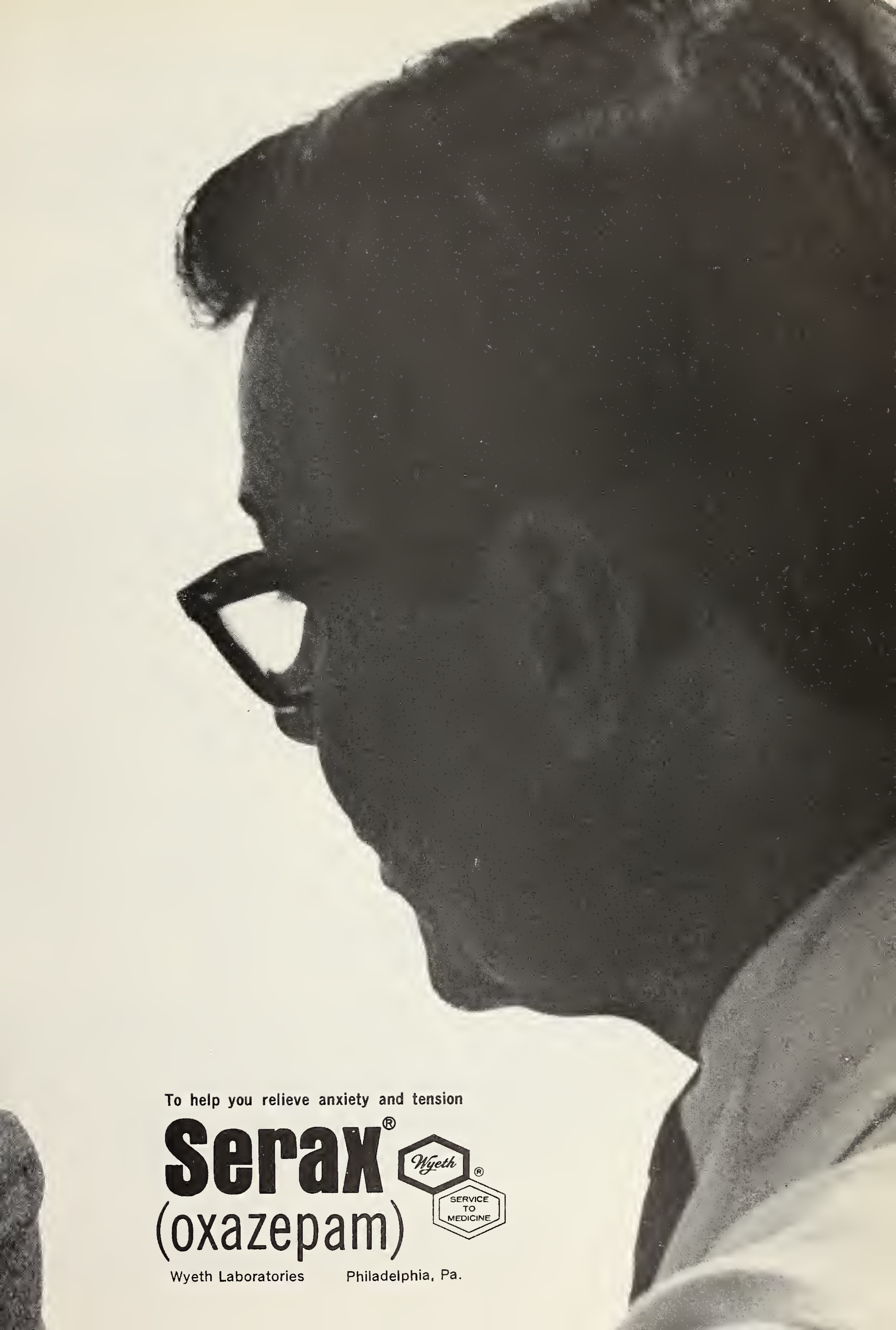

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without providing for adequate procedural safeguards set forth in the medical staff bylaws.

6. The governing board is ultimately responsible for the quality of medical care but the fulfillment of this responsibility must be delegated to the medical staff. The medical staff should regularly submit reports to the governing boards of its professional activities providing for comparison with accepted standards of patient care.

7. The bylaws of the medical staff should be approved by the governing board, should provide for the organizational principles outlined above, and should accurately reflect the actual operation and organization of the medical staff.

PLACEMENT WANTED

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Report on Northeast Regional Conference on Nutrition Education

This two day conference was held in New Haven to celebrate the 50th Anniversary of the Connecticut Nutrition Council. The theme was "Increasing the Effectiveness of Nutrition Education." Throughout the program the various speakers and panelists brought out the four basic concepts of Nutrition Education developed by the Interagency Committee on Nutrition Education for the National Nutrition Education Council hed in Washington D. C. this past February. They are:

1. Nutrition is the food you eat and how the body uses it.
2. Food is made up of different nutrients needed for growth and health.
3. All persons, througout life, have need for the same nutrients, but in varying amounts.
4. The way food is handled influences the amount of nutrients in food, its safety, appearance, and taste.

The first speakers emphasized the fact that to get better nutrition to the people first they must motivate a change. This is a very large job. We found that some of the ways to do this was through newspapers, magazines, radio and television. The most effective ways are through short narratives and appealing pictures. The greatest problem is to be sure the articles published and shown are accurate.

Also brought out by Nevin S. Scrimshaw, M.D., Ph.D. of M.I.T. in this conference was the fact that science and research was far ahead of the material known by the people in general and we must work to get this knowledge to all the people.

Some of the current efforts in communicating nutrition to the people are the food stamp plan, the child nutrition program (school lunches included), and ambulatory service programs.

The meeting was concluded by two speakers. George Christakis, M.D. stressing the need of nutrition and also the need to have more nutrition courses taught to the students in medical schools. The M.D.'s are the ones to designate the types of nutrition the people are to follow and they have not been adequately trained for this unless they take a graduate course in nutrition. Finally it was emphasized by Evelyn B. Spindler, Ph.D., nutritionist that we must coordinate our various nutrition programs to have them effective.

After the meeting was concluded a tour of the Yale—New Haven Medical Center was offered.

Mrs. Clarence Harwood

AMPAC WORKSHOP
Washington, D.C. — June 2 to 4, 1967

Those who planned this workshop provided an inspiring and informing program and must have felt rewarded with the results. Over 500 representatives from the 50 states attended and were overwhelming in their enthusiastic reception of the speakers.

Miss Susan Walker, Vice-chairman of the Conservative and Unionist Party of Great Britain gave a detailed report of the forming, developing, and current structure of her Party which has been in existence 100 years. She also explained how a candidate is chosen: by first submitting an application including detailed information about his life to date, providing three references, then been interviewed by an Advisory Committee on Candidates, working for the Party, then waiting until a vacancy occurs—one which the Committee considers suitable for him. Also she emphasized that young people are encouraged to take an active part in party policies.

A panel consisting of Senator George Murphy of California, Senator Walter F. Mondale of Minnesota, Representative Bob Wilson of California, and Representative Don Fuqua of Florida, gave their views on various questions posed by the moderator, Dr. Hoyt D. Gardner. They all agreed that the greatest assistance in the campaign came from women who worked as telephone callers, gathering together groups, providing coffee hours in their homes—Mr. Wilson mentioned *WOW* (Women on the Warpath), a group that worked for him. Mr. Murphy said that during the Primary campaign he didn't talk to anyone else but women. Mr. Fuqua said that one woman volunteer is worth five men. They all agreed that in fund raising, the most valuable method is to get the widest possible number of people to give the most they can. They mentioned a One Dollar Box Dinner, $10 sustaining party membership, one dollar per member (Mr. Wilson mentioned obtaining $8000 in this way). Specifically to doctors their words of advice were: *Be knowledgeable, Spread your influence, The public respects your opinions, Be interested in your Government and your Country—it belongs to you, Let your Representatives know your wishes, Be a self-starter in Politics,* What really counts in government is Quality-Sophistication-Integrity.

It was made clear by the various candidates that money is very important both to win an election and to carry on the duties of the office. They were all recipients of candidate support from Ampac and State Pacs and all expressed gratitude for the support. Rep. Robert Michel of Illinois urged doctors not to lose interest in politics because Medicare was passed. He said many more Health bills will be coming and will require the support or opposition of doctors. He did request that supporters do not inhibit candidates. He pointed out that there are powerful utilities seeking laws, but many more users of utilities (voters) also that there are many doctors, but many more patients (voters).

Robert Novak, National syndicated columnist, expressed his views on Foreign Policy. In Vietnam, he said, "escalation of the war at this time can only mean chemical or nuclear warfare." He said, "it is impossible to achieve military victory." "There is a possibility of negotiating for peace, but this is not likely before the 1968 election since it is apparent that they (North Vietnamese) think they could do better with a new president."

He also stated that not much change is expected in the general economic situation.

Rep. Gerald Ford of Michigan reported on current activity in Congress and urged that we learn facts on candidates and use judgement in supporting them. He said "A Government big enough to take everything it wants, is big enough to take everything we have."

Obviously it is impossible to report everything that was said. So much information was packed into the two-day conference and so much of it seemed vital. There were excellent reports from members of the AMPAC Board; four films, "A Congressman's Two Year Campaign for Re-election," "Managing the Campaign," "The Use of Volunteers in a Political Campaign," "Public Relations of a Political Campaign,"; and a Political Management Game put on by Mr. William Roberts of the Spencer-Roberts, Associates in which all members of the Conference participated.

In short it was urged that all doctors and their wives become members of AMPAC and COMPAC. Although this is a quiet year, next year will find the need for candidate support even greater. 1968 is expected to be a banner election year. The cost of election campaigns increases constantly due largely to the various media of communication. Doctors can no longer sit back and "Let George do it! The competition for legislation is too great!

Friederike H. Richards

Around The State

New Haven County

ORIENTATION OF PROVISORY MEMBERS

New Haven County Medical Association

The New Haven County Medical Association held an indoctrination meeting for provisory members on the night of June 13, 1967, at the Castle Memorial Building in Waterbury. This was preceded by a social hour and dinner for the provisory members, the officers of the Association, the Board of Governors and special guest participants. Fourteen physicians were presented with membership certificates.

Dr. Michael Gualtieri, Chairman of Committee on Credentials and Orientation of Waterbury presided after dinner. Speakers explained the Organization and role of our County, State and American Medical Associations. Dr. Samuel Rentsch, President of Connecticut Medical Examiners Association and Attorney Frank Healey, Jr., of Waterbury touched on the legal aspects of medical practice. The latter also emphasized the relationship which exists between the Bar and the Stethoscope.

The last participating guest was the Rev. J. C. Fanning, Pastor of St. John of the Cross in Middlebury. Father Fanning's understanding approach to the problems of critical illness with its moments of stress and anxiety for the patient and his family, made a deep impression on our audience. With his benediction a very profitable evening came to a close.

Respectfully submitted,
H. A. Levin, M.D., *Clerk*

Doctor's Office

Edmund J. Brennan, M.D., announces the relocation of his office for the practice of obstetrics and gynecology to the new Medical Building, 573 North Church Street, Naugatuck.

Jachin B. Davies, M.D., announces the removal of his office for the practice of obstetrics and gynecology to University Towers, 100 York Street, New Haven.

Benjamin J. Feola, M.D., announces the opening of an office, presently on Thursdays only, for the practice of obstetrics and gynecology at 37 Commerce Street, Clinton.

Victor R. Grann, M. D., announces the opening of an office for the practice of internal medicine with subspecialty of hematology and oncology at 98 Hoyt Street, Stamford.

Frederick Kessler, M.D., announces the relocation of his office for the practice of allergy to University Towers, 100 York Street, New Haven.

Gerald Krosnick, M.D. and Stanley R. Lavietes, M.D., announce the association of Dr. Carl Cassin in the practice of obstetrics and gynecology at 2 Church Street South, New Haven and a new additional office at 299 Washington Avenue, Hamden.

John F. Paget, M.D., Allan E. Bayless, M.D. and Harry P. Engel, M.D. announce the relocation of their office for the practice of neurosurgery to the Columbia Towers Professional Building, 50 Ridgefield Avenue, Bridgeport.

Special Notices

COURSE IN POSTGRADUATE GASTROENTEROLOGY

November 2, 3, 4, 1967

The American College of Gastroenterology announces that its Annual Course in Postgraduate Gastroenterology will be given at The Biltmore in Los Angeles, Calif., on November 2, 3, 4, 1967.

The faculty for the Course will be drawn from the medical schools in and around Los Angeles. The subject matter to be covered in the Course, from a medical as well as surgical viewpoint, will be, essentially, the advances in diagnosis and treatment of gastrointestinal diseases and a comprehensive discussion of diseases of the esophagus, stomach, pancreas, liver and gallbladder, colon and rectum. In addition there will be individual papers and films of interest.

For further information and enrollment write to the American College of Gastroenterology, 33 West 60th Street, New York, N. Y. 10023

In Memoriam

Brewer, Timothy F.—West Hartford; Yale School of Medicine, 1926. Dr. Brewer was a prominent internist and cardiologist in the Hartford area. He was on the medical staffs of St. Francis and McCook Memorial Hospitals. He served as lieutenant commander (Medical Corps) for the U. S. Naval Reserve during World War II in California and Japan. He was also examining physician for Draft Board #2 during that war. He was a member of the Hartford Medical Society, the Hartford County Medical Association, the Connecticut State Medical Society, the American Medical Association, and the American College of Physicians. Dr. Brewer died May 31, at the age of 65.

Hamilton, Charles K. — Brookfield; Columbia College of Physicians and Surgeons, 1932. During World War II, Dr. Hamilton served with the Army's Nineth Evacuation Hospital, organized at Roosevelt Hospital in New York. He held staff appointments in urology at French and Goldwater Hospitals, Cornell University Medical College, Bellevue and Doctors' Hospitals, all in New York. He was an attending urologist at Danbury Hospital and senior attending urologist at Bellevue Hospital. He was certified by the American Board of Urologists. Dr. Hamilton held teaching appointments at both Cornell Medical College and Bellevue Hospital. He was a member of the Danbury Medical Society, the Fairfield County Medical Association, the Connecticut State Medical Society, the American Medical Association, the New York County Medical Association, and the American Urological Association. Dr. Hamilton died June 6, at the age of 62.

Heublein, Gilbert W.—Hartford; Yale School of Medicine, 1934. Dr. Heublein was a noted radiologist and businessman in the Hartford area. He was a member of the senior radiological staff at Hartford Hospital and was chief radiologist at the Institute of Living in Hartford. Dr. Heublein was a visiting clinical professor of radiology at the Jefferson Medical College and Medical Center in Philadelphia and had lectured throughout North America. He was a member of the Hartford County Medical Association, the Connecticut State Medical Society, the American Medical Association, and was a fellow and diplomat of the American College of Radiology. Dr. Heublein had a major interest in the ownership of the family-founded liquor and food company, Heublein, Inc., which was based in Hartford. Dr. Heublein died May 27, at the age of 58.

Beatniks: Up, Down and Off

CHICAGO—Not all beatniks are bad, says a psychiatrist in a current American Medical Association publication.

In fact, beatnikism may be just another way for a teenager to find groups with similar, sympathetic interests on his way to adulthood.

Writing in a recent issue of the Archives of General Psychiatry, published by the AMA, Jules Masserman, M.D., classifies beatniks into three groups:

Up-Beatniks—The best of the lot, says Dr. Masserman, who is professor of psychiatry at Northwestern University, Evanston, Ill. Even with their occasional beards, tresses, play-readings, placards, proclamations, and protest marches, they are "Basically earnest, energetic, intelligent, and well intentioned."

They are a help "in prodding us oldsters to review our smug hypocrisies and revise our medieval customs and conduct," Dr. Masserman said.

Down-Beatniks—Articulate in condemning the inequalities and injustices of society, often with some courage and justification. They are strident and obnoxious in speech and manner, but the outlook for their improvement is often favorable.

"With further maturity and increasing wisdom, most of them become good citizens, competent parents and sometimes even staunch Republicans," said Dr. Masserman.

The Off-Beatniks—These are the more seriously erratic, troubled, and troublesome misfits. Despite their pretensions, they contribute little that is truly constructive or original to our culture.

What makes a beatnik? The teenager is looking for "identity" in a world of great complexity, Dr. Masserman explained.

"The late adolescent may spread himself thin trying to be simultaneously a dutiful child, a brilliant scholar, a winning athlete, a popular leader, a potent lover, a seductive nymph, a cynical sophisticate and a dozen other incompatible alter egos."

Most youngsters seek status in groups offering support, with certain patterns of dress, modes of speech, and stereotyped musical tastes.

Dr. Masserman said most such cliques are harmless and may even be beneficial as interim experiences. He cautions:

"The dividing line is this: When an adolescent becomes so immersed in extracurricular activities as to neglect his education, physical health and broader social development, or when he advocates 'sports' that endanger others, such as drag racing, or when he promotes public obscenity, sexual arrogance and physical violence, or experiments with excessive amounts of alcohol or drugs, then therapy is necessary."

Tandearil®
oxyphenbutazone

Therapeutic Effects: Tandearil is a nonhormonal compound which may rapidly resolve inflammation and help restore normal joint function. Its action does not affect pituitary-adrenal function or impair immune responses. Its value in osteoarthritis is especially noteworthy because this disorder responds inconsistently to steroids and is often resistant to salicylates. Further, indomethacin is limited only to osteoarthritis of the hip, whereas oxyphenbutazone is effective in all forms of the disease.

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage. Make regular blood counts. Discontinue the drug and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: The initial daily dosage in adults is 300-600 mg. in divided daily doses. When improvement occurs, dosage should be decreased to the minimum effective level; this should not exceed 400 mg. daily, and is often achieved with only 100-200 mg. daily.

For complete details, please refer to full prescribing information. 6562-VI(B)R

Availability: Tablets of 100 mg.

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COMMENTS ON THE 1967 CONNECTICUT PHYSICIAN'S ART EXHIBITION

In general, the Art Exhibit seemed well received again this year. There were 96 art works entered, and the facilities for displaying this exhibit were improved over last year. The art work included a wider range of media this year. This was especially true in the sculpture section.

The awards given were as follows:

"BEST IN SHOW" went to Dr. James A. Riley of New Haven. This was an untitled oil painting.

JOHN M. FREIHEIT AWARD went to Dr. Ralph Parker of Bridgeport for a water color entitled "Serenity."

In the *professional category* the first prize was won by Dr. W. W. Wright of West Hartford for an oil painting entitled "Mr. Marks."

Second Prize to Ester McAlenney of Woodbridge, for a water color entitled "Fleurs D'Ete."

Honorable Mention in this category went to Ruby Gilman of Storrs, Connecticut for a painting entitled "Old South Wharf."

Amateur Water Color & Pastels:

First Prize went to Liesel Braun of Trumbull for a picture entitled "Fiesta."

Second Prize to Dr. Donald Morrison of Hartford, entitled "42° 39′ N-70° 41′ W."

Honorable Mention to Dr. John Meyer of Putnam for a painting entitled "East Gloucester."

Collages, etc, First prize went to Dr. Beatrice Gordon of West Hartford for "Frills & Pills."

Second Prize to Charlotte Moss of Hamden, for "Maine-ia."

Honorable Mention to Justin Gordon of West Hartford entitled "Sun Tanning."

Black & White Category:

First Prize Kathleen VonGraevenitz of New Haven, picture entitled "Marsh Bird."

Second Prize to Dr. Nicholas Giosa of Wethersfield "Lithographs with Words."

Ceramics Award to Mrs. Norma Jonas of Fairfield "For Thanksgiving."

Sculpture—Professional Category:

First Prize to Mrs. Samuel Rentsch of Derby, "Madonna and Child."

Sculpture—Amateur Category:

First Prize went to Mrs. Ruth Lidz of Woodbridge, entitled "Egghead."

Second Prize, went to Dr. Peter Gram of Manchester for "Anlage."

Honorable Mention to Philip Corso, M.D. of Bridgeport entitled "14 Century Plastic Surgery."

Photography:

First Prize to K. A. Oster, M.D. of Bridgeport entitled "Water Taxy."

Second Prize to John Woodworth, M.D. of Moosup, entitled "Menemsha Harbor."

Honorable Mention to K. A. Oster, M.D. Bridgeport, entitled "Klong Scene."

Children Category:

First Prize to Harold Gordon of West Hartford entitled "Fruit." (father Yale Gordon M.D.)

Second Prize to Barry Gordon, of West Hartford, entitled "Snow Flakes" (father Yale Gordon M.D.)

Honorable Mention to Wendy Fairlee of Hartford, entitled "Summer." (father C. W. Fairlee M.D.)

Oil Amateur:

First Prize to Kathleen VonGraevenitz of New Haven, entitled "Lake Michigan."

Second Prize to Stewart Petrie, M.D. of Derby, entitled "Evening on Spanish Steps."

Honorable Mention to Morton Glasser, M.D. of Lebanon entitled "Seated Woman."

Oil Beginners:

First Prize to Norma Jonas of Fairfield, entitled "Venice."

Second Prize to Lillian Della Selva of Bridgeport, entitled "Farm in Winter." (Mother of Mrs. Anthony Cipriano, Hamden, the incoming Pres. of Woman's Aux. to Connecticut State Medical Society).

The judges were:

Gail W. Martin—Prof. of Art—Hartford Art School of the University of Hartford. Mem. Conn. Water Color Soc., and Conn. Academy of Fine Arts.

Mitchell Pappas—Assoc. Prof. Fine Arts—Trinity College, Member Conn. Water Color Society and Conn. Academy of Fine Arts.

Ethel Stauffer—Hamden Painter & Teacher—Past Pres., New Haven Paint & Clay Club, also member Conn. Academy Fine Arts, and Penna. Academy of Fine Arts.

The Art Association wishes to thank all those concerned, especially the Connecticut State Medical Society, and Woman's Auxiliary, and a thank you is also extended to the New Haven County Medical Association for their presentation of the "Freiheit Award." It should be known, that the Art Committee is quite receptive to any suggestions regarding improvement of the show and its format. It seems to be the feeling of the Art Association, as well as many others, that interest and attendance at the State Society meeting is improved by this Art Show.

Stewart J. Petrie, M.D. *President*
Connecticut Physicians Art Association

NEW BOOKS IN REVIEW

THE THYMUS: Experimental and Clinical Studies. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol, and Ruth Porter, M.R.C.P. Little, Brown and Company, Boston, 1966. 538 pp. with 96 illustrations. $15.00.

Reviewed by: LOUIS H. NAHUM

The symposium was held in Melbourne, Australia. It should help greatly the understanding of the thymus and how the subject may be taught and also contribute to scientists doing research on this crucial subject. It should be emphasized that the symposium was held in August of 1965 and since then much new material has appeared such as Professor A. Whites work on thymosin, a thymic hormone causing lymphocyte proliferation as well as an inhibitor of lymphocyte proliferation; work which will have far reaching basic science and clinical implications. Then also there is Van de Velde and Friedman's study on thymic myoidzellen in myasthenia gravis which has recently appeared.

But one does find here many crucial suggestions about the thymus. For example this gland is the center of lymphoid cell proliferation. Lymphoid cells emerge from the thymus and migrate to second-level lymphoid organs. The outflow of these cells represents the main or only source for the introduction of new immune patterns in the organism. Plasma cells may be derived from lymphocytes through antigenic stimulation or some equivalent.

The twenty six contributors are world famous and one Sir Macfarlane Burnet a Nobel prize winner. There are stimulating discussions after each paper and an excellent summary of the whole work by Burnet.

APPRAISAL OF CURRENT CONCEPTS IN ANESTHESIOLOGY, Volume 3. Edited by John Adriani, M.D., Professor of Surgery, Tulane University School of Medicine, New Orleans, Louisiana. The C. V. Mosby Company, St. Louis, 1966, pp. 522, cloth $10.85.

Reviewed by: JOHN D. MURPHY

This volume in manual form was compiled by members of the Anesthesia Department of Charity Hospital, New Orleans, Louisiana under Dr. John Adriani. The topics presented are in the form of review summaries of the literature as were those contained in the first two volumes of this book. Fifty subjects are here treated by twenty-eight contributors, an expansion of five over the previous editions.

The subject matter of each treatise is a condensation of the recent medical literature on said topic blended with (in most cases) a brief historical review and/or basic introduction. Each has a limited bibliography, although most references are fairly current.

The first dozen chapters deal with pulmonary physiology and aspects of inhalation therapy. The remainder range from antineoplastic drugs and anesthesia to the time-worn physiologic changes of pregnancy. Scattered along the way are several excellent discussions, including a three-chapter series on uptake, distribution and elimination of volatile anesthetics, a chapter on cardiac defibrillation and cardioversion, and a brief, but timely section on fibrinolysins and antifibrinolysins.

While far from an exhaustive review of any of the topics included, this volume would seem to fill nicely the need for updating the literature in the realm of many anesthetic and para-anesthetic problems. Such a compilation of reviews of subjects that are of particular interest to anesthesiologists, that include the early as well as the current thinking is a ready source of valuable information.

This handy little book is well bound with easily readable type and should be within easy reach of every practicing anesthesiologist. As a companion to the Yearbook and Surveys of Anesthesia, Volume 4 of "Current Concepts" should be warmly welcomed on its publication.

GRAY'S ANATOMY by Charles M. Goss, M.D., Lea & Febiger, Philadelphia, 1966, 28 edition, 1182 illustrations, 1464 pages, $22.50.

Reviewed by: LOUIS H. NAHUM

This "Bible of Medicine" now one hundred and eight years old is actually new. Every page has been rewritten to some extent so that it is practically a new book. The new Nomina Anatoma has been adopted. Don Alvarado's art shows itself in many drawings and adaptations of others from the literature with new labels and pictorial initials beginning each chapter so that this book is modern, fresh and clear.

The author has increased eponyms largely to maintain an element of history of ideas for those teachers of anatomy that have a strong feeling for medical history.

This edition like the first one in 1858 shows a continuing special effort to organize the material in a way that can be adopted for study in any degree of depth. Even what is left out in abbreviated courses in anatomy is here available during the course and is also accessible for review when a student is preparing for an examination.

There are certain special features in this edition such as a rewriting of lymphatics and veins, photographs of Dr. John Gourgott in the chapter on surface anatomy. The entire book has been reset with new type in a two column format.

In every respect this is the best edition published so far containing embryology and developmental anatomy as well as beautiful drawings in color. It has been a bible for thousands of students for over a century and remains a wonderful item for student and physician for today and tomorrow.

IUSCULAR AFFERENTS AND MOTOR CONTROL, *Nobel Symposium I. Edited by Gagnar Granit. John Wiley & Sons, New York, London and Sydney, 1966, 466 pp. $20.00.*

Reviewed by: LOUIS H. NAHUM

The 1st Nobel Symposium is an experiment which all ope will flourish and prosper. It keeps the number of active articipants modest, the subject reasonably restricted and a areful matching of participants to subject matter. Several nportant contributions to financing this adventure made t possible. The Swenska Handelsbanken made an extremely andsome offer of placing at the disposal of the Symposium Sodergarn" a center of recreation and residential courses n the island of Lidingo, twenty minutes by car from Stockolm. Sodergarn provided the Symposium with board and odgings, a lecture hall, conference rooms, lovely weather, pen country and delightful walks along the shore of the skrikefjord.

The time of this Nobel Symposium links up with one eld in 1961 at Hong Kong on Muscle Receptors and this Nobel effort included "Motor Control" meaning the role of he central nervous system. A comparison of the two symposia held five years apart shows that a great deal has been dded to the subject, new experiments, fresh ideas and contructive thinking. The discussion however was limited for the nost part to connecting muscle spindle anatomy with reent physiological work.

We all hope of course that discussing physiological facts nd theories as is done in this excellent volume will lead to etter medical treatment and the ideas presented in this ook should help physiologists to suggest to medical colleges s well as pursue the meaning of these basic ideas to their pplication. However, for the present, this book belongs on he shelf of neurophysiologists and the occasional neurologist ike Dr. Gilbert Glaser of Yale, a participant in this symposium who should be the bridge between basic science and ractical medicine.

CLINICAL MANAGEMENT OF BEHAVIOR DISORDERS IN CHILDREN. *Harry Bakwin and Ruth Morris Bakwin, 3rd edition. W. B. Saunders Company, Philadelphia and London, 1966, 652 pp., illustrated. $14.50.*

Review by: LOUIS H. NAHUM

The general plan in this edition is unchanged over that of 1960. The chapter on child development and the section on developmental disorders have been greatly expanded because of its wide influence on childhood behavior. There is a bibliography at the end of each chapter but very few new ones have been added since the 1960 edition. Past contributions to this extremely important field came primarily from psychoanalysis, psychiatrist, psychologist, the social worker, teacher and of course the worried parent. Apparently the Bakwins who are pediatricians have bypassed psychoanalysis in this volume since the whole area of ego psychology, instinct, the oedipus complex, the nature of aggression receives hardly any treatment.

It is true that a variety of new developments have undermined what was thought of as a unified theory of behavior. The animal behaviorist, the geneticist, the learning theorist, the developmental neurologist, the experimental psychologist and above all the pediatricians have opened anew and brought some understanding to human maturation and behavior. There is now increasing attention to critical periods, imprinting, motivation learning, the functional development of language and these have weakened the rigid mold into which ego psychology brought the problem of behavior disorder in children.

The field of behavior disorders in children as a specialty in Pediatrics is increasingly based on the fact that early recognition and treatment of such illnesses can alleviate symptoms and may possibly go far toward helping the child to a happier and more effective adulthood. This may be because workers in the field are developing a better understanding of the broader biologic basis of behavior. It is proper that more emphasis should be placed on the preventive aspects of illness. Most child psychiatrists agree that learning and motivation is a complex of genetic factors, physiologic processes, environment and social exposures and on the maturation and timing of crucial events in the life of the individual. The problem of the underprivileged child, the scholastic underachiever, the mentally retarded child, the juvenile delinquent and a host of behavior problems are recognized and dealt with by the authors in a wise manner obviously the result of long and careful experience. It is comprehensive and full of common sense.

If no basic philosophy and unified concept is apparent it is because we still labor with serious gaps in our basic information about the developing child. The Bakwins have shown us however that enough is known to be useful in our understanding, diagnosis and management of many of the behavior problems of childhood. The book reads so easily, the sentence structure so lucid that many of the sections could readily be understood by the parent as well as the physician.

BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Black Market Medicine. Edited by Margaret Kreig. Prentice-Hall, Inc., Englewood Cliffs, 1967, 336 pp. $5.95.

Physiology of Muscular Exercise. Edited by Carleton B. Chapman, M.D. American Heart Association, Monograph Number Fifteen, 1967. 226 pp. $3.00.

Christianity And Medical Science. Edited by Charles T. Bingham, M.D. Salem Books. 92 pp. $5.00.

Cardiovascular Surgery 1966. Edited by C. Frederick Kittle, M.D. American Heart Association, Monograph Number Sixteen, 1967. 243 pp. $3.00.

The Future of the AMA Group Disability Insurance Program

Several months ago, some 40,000 members enrolled in the AMA's Lifetime Benefits Disability Insurance Program were notified that, as of August 31, 1967, the five-year agreement between AMA and the Continental Casualty Insurance Company would expire and would not be renewed by CCIC unless extensive revisions in the program were effected. One such revision would cancel the policies now held by many older members of the Association, and make it impossible for many other members to enroll in the future. The Board of Trustees referred this matter to the House of Delegates for study and recommendation, and, on June 22, 1967 at Atlantic City, the House adopted the following Reference Committee Report which is to be implemented by the Board.

American Medical Association House of Delegates

Report of Reference Committee I

Presented by: Norman H. Gardner, M.D., Chairman

Mr. Speaker and Members of the House of Delegates:

Your Reference Committee commends the Board of Trustees for its objectiveness and willingness to seek the advice and guidance of the House of Delegates in a matter of great personal interest affecting more than forty thousand participants in the AMA Members Group Disability Insurance Program. In open hearings your Reference Committee received the testimony of numerous representatives of insurance carriers, actuaries, brokers, members of the Association, delegates, and members of the Board of Trustees. Some of the testimony was conflicting. While it was stated that the present program is actuarially unsound, your Reference Committee was impressed by the fact that other testimony stated that any unsoundness that existed could be corrected by an active promotional program aimed at adding a substantial number of subscribers to the program. The heavy weight of evidence as noted in the Reference Committee hearings would indicate that a large majority of this House, representatives of their state associations and constituent societies, would favor the continuation of the program as presently constituted as to premiums and benefits. In executive session, your Reference Committee gave careful consideration to all proposals and suggestions that were offered. Your Reference Committee has reservations about a condition that the contract be mutually binding upon both parties for a period of five years. However, it believes that any pitfalls can be minimized by the adoption of appropriate safeguards. Such safeguards should establish the control of the Board of Trustees or its designee over the program.

Your Reference Committee, therefore, recommends that the House of Delegates authorize the Board of Trustees to follow the second alternative in Report P and make every effort to continue the AMA Members Group Disability Insurance Program with the same premium-benefit structure.

It also recommends that the House of Delegates approve the following guidelines to aid the Board of Trustees in negotiating and executing the necessary contracts and in the future operation of the program.

1. The contract should provide ample assurance that disability claimants will be treated equitably and justly. It should also assure the continuation of a sound program under the supervision of the Board of Trustees.
2. The carrier should guarantee benefits and premiums for a period of at least five years in order to assure the stability of the program.
3. Promotional literature should be approved in advance by the Board of Trustees or its designee. Such literature may be distributed in the name of the carrier, the administrator, or the Board of Trustees or its designee. All measures within the bounds of dignity and ethics should be utilized to promote the program.
4. A continuous on going review of the entire program should be maintained. The insureds and other members of the AMA should be made aware that such an ongoing review may reveal in the future the necessity for a revision of the program at the end of the five-year period.
5. Information regarding the operation of the program, its financial aspects and the processing of claims should be available to the Board of Trustees for its review at any time.
6. The AMA Disability Insurance Review Committee should be continued and should provide a mechanism for claims review.

Your Reference Committee recommends that the House of Delegates reaffirm its confidence in the discretion of the Board of Trustees in applying these guidelines as an aid in negotiating the most favorable contract for the benefit of members of the American Medical Association.

AMA Evaluates Oral Contraceptives

Oral contraceptives have caused some adverse reactions, but no really serious side effects can yet be attributed directly to their prolonged use, says a report of the Council on Drugs of the American Medical Association in the current Journal of the AMA.

Further study is needed of the oral contraceptives' complex biochemical effects, the Council said.

In the meantime, the physician has been given an "uneasy responsibility." He must use his professional judgment and be apprised of latest drug information when prescribing these pharmaceutic preparations in order that his patients may derive their full benefits.

This has broadened the meaning of therapeutics, the Council pointed out. These drugs are given to healthy people, not sick ones, and "any possible hazards connected with their use must be weighed against their expected benefits, perhaps more critically than has ever been the case before."

"A variety of adverse reactions to the oral contraceptives have been described. Some of these effects . . . are unquestionably drug-related; fortunately, most of these are not of a serious nature, although they may be annoying to the patient.

"More serious effects that have been ascribed to these preparations are seen rarely, and causal relationships have not as yet been established," the report said.

Some of the side effects:

Breakthrough bleeding or spotting appears to be somewhat greater with the combination progestogen-estrogen type of contraceptive preparation; its occurrence with the newer, sequential-type preparations usually is related to missed doses. The frequency of breakthrough bleeding with the progestogen-estrogen combinations tends to diminish with successive cycles of therapy.

Failure of menstrual bleeding may occur with all oral contraceptives. The frequency varies; when it occurs, the next cycle of treatment is begun seven days after the last tablet was taken.

The failure of menstrual bleeding after two consecutive cycles may indicate a possible pregnancy.

Decreased glucose tolerance has been reported in women receiving the progestogen-estrogen combinations; diabetic responses to glucose tolerance tests and worsening of diabetic conditions also have been reported. It is likely that similar effects may be produced by the sequential preparations, although definitive information is lacking.

There is no proof that oral contraceptives cause circulatory complications; however, physicians should use care in prescribing them for women with vascular disease until more information is available.

Central nervous system and ocular complications have been ascribed to these preparations. "Although evidence is not sufficient to establish a cause-and-effect relationship, therapy should be stopped and the status of the patient carefully evaluated if any symptoms or signs suggesting cerebrovascular or ocular changes appear," the report said.

Headache may occur with any of the preparations. Nervousness, irritability, lethargy, and depression have all been attributed to oral contraceptives.

"These symptoms are influenced by many emotional factors and occasionally may cause the patient to discontinue medication," the report said. "On the other hand, preexisting similar complaints may be relieved in some patients when they are taking oral contraceptives."

Abnormalities in liver function tests have been observed, but such changes usually are not clinically significant. "Although changes in liver function may be expected to be reversed when the medication is discontinued, caution is necessary when oral contraceptives are used in patients who have a history of impaired liver function," the report said.

Excessive weight gains have been reported in some women, mostly in association with the older contraceptive preparations that contain larger doses of estrogen. The lower dose preparations are less likely to produce significant weight changes.

Nausea has been a frequent complaint during the first cycles of therapy, but usually diminishes as therapy is continued.

"The possible relationship of oral contraceptives to cancer is controversial," the report said. "Theoretically, some risk is incurred with prolonged estrogen therapy; however, extensive studies have revealed no evidence of carcinogenesis in association with the use of oral contraceptives."

Oral contraceptives are of two types: the progestogen-estrogen combinations, introduced in 1960, and the sequential preparations, introduced in 1965.

All of the progestogen-estrogen combinations are used in the same way; counting from the first day of menstruation, a single daily dose is taken from the 5th through the 24th day of the cycle. Withdrawal bleeding usually occurs within three to four days after the last dose.

"The progestogen-estrogen combinations are the most effective medical means for preventing conception yet devised. The available data indicates that pregnancy will occur in less than 1 per cent of women who use this method properly," the report said.

The sequential-type oral contraceptives are given for 20 or 21 days in each treatment cycle, depending upon the preparation. Counting from the first day of withdrawal bleeding, the estrogenic component is taken in a single daily dose for 15 or 16 days from the 5th through the 19th or 20th day of the cycle. The mixture of the estrogen and the progestogen is taken for the next five days. Withdrawal bleeding usually begins two to five days after completion of the cycle of medication.

"Although these preparations also are highly effective, the available information indicates that strict adherence to the treatment schedule is more critical than is the case with the progestogen-estrogen combinations," the report said. "In the majority of cases of reported pregnancies, the patients missed taking tablets during the period of estrogen administration.

Supplementary Oxygen Improves Hemiplegic Rehabilitation

When supplementary oxygen is given to stroke patients with left hemiplegia (left-side paralysis), some of the physical and mental impairments associated with hemiplegia are temporarily alleviated.

Amelioration of the characteristic fatigue and confusion of hemiplegia makes rehabilitation an easier task, reported a group of investigators from New York University Medical Center, New York City.

The report by Albert Haas, M.D., Yehuda Ben-Yishay, Ph.D., and Leonard Diller, Ph.D., was presented at a scientific session of the American Medical Association's 116th Annual Convention.

Investigations conducted by Dr. Haas and his colleagues sustained a hypothesis that the easy fatigability and impaired mental functioning of hemiplegic patients is partially caused by chronic, low-grade hypoxemia (oxygen hunger). The hypoxemia is assumed to result from the partial impairment of respiratory function after the stroke.

The study was carried out with 98 patients at the Institute of Rehabilitation Medicine, New York University Medical Center. All the patients had suffered a cerebral vascular accident in the right side of the brain, resulting in left-sided paralysis, and all were undergoing rehabilitation. Patients with right hemiplegia were excluded from the study because of the high incidence of communication difficulties among them.

A number of physiological and psychological tests were administered in the laboratory, with each patient undergoing the full battery of tests three times.

The first series of tests provided baseline scores; the second series was run while the patients inhaled 100 per cent oxygen; the third test, without oxygen, served as a control and to indicate any remission in symptoms due to oxygenation.

Physiological testing indicated various degrees of impairment in pulmonary functioning, blood gas composition, diffusion and perfusion. The patients had abnormally high respiratory rates, and their oxygen consumption during exercises was 50 per cent higher than in a comparable group of healthy persons.

Many of the functional disturbances were mitigated while the patients breathed 100 per cent oxygen, the investigators said. Amelioration did not extend significantly beyond the time of active oxygen inhalation.

Psychological studies showed that oxygen inhalation improved significantly the ability of many patients to perform tasks involving sensory perceptual and sensory motor functions. Verbal performances did not improve under oxygenation.

Allergist Describes Investigations New Concepts Of Hay Fever

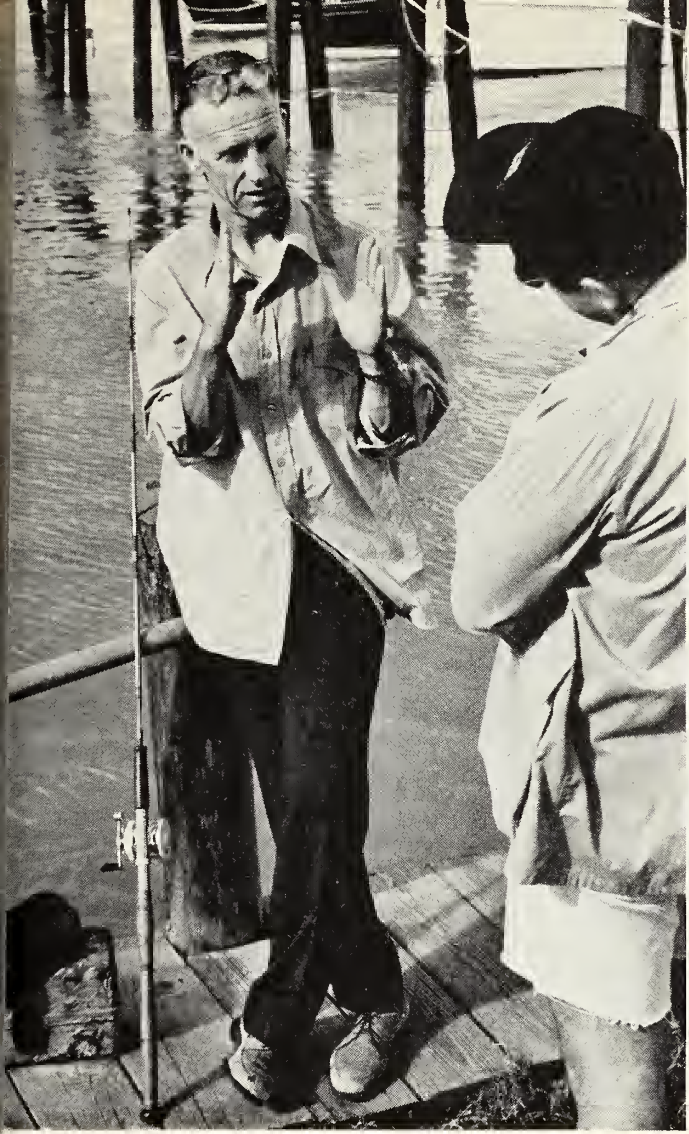
An allergist's continuing investigation of hay fever and its mechanisms have led him to some unique concepts of the disease, which he shared with physicians at the annual convention.

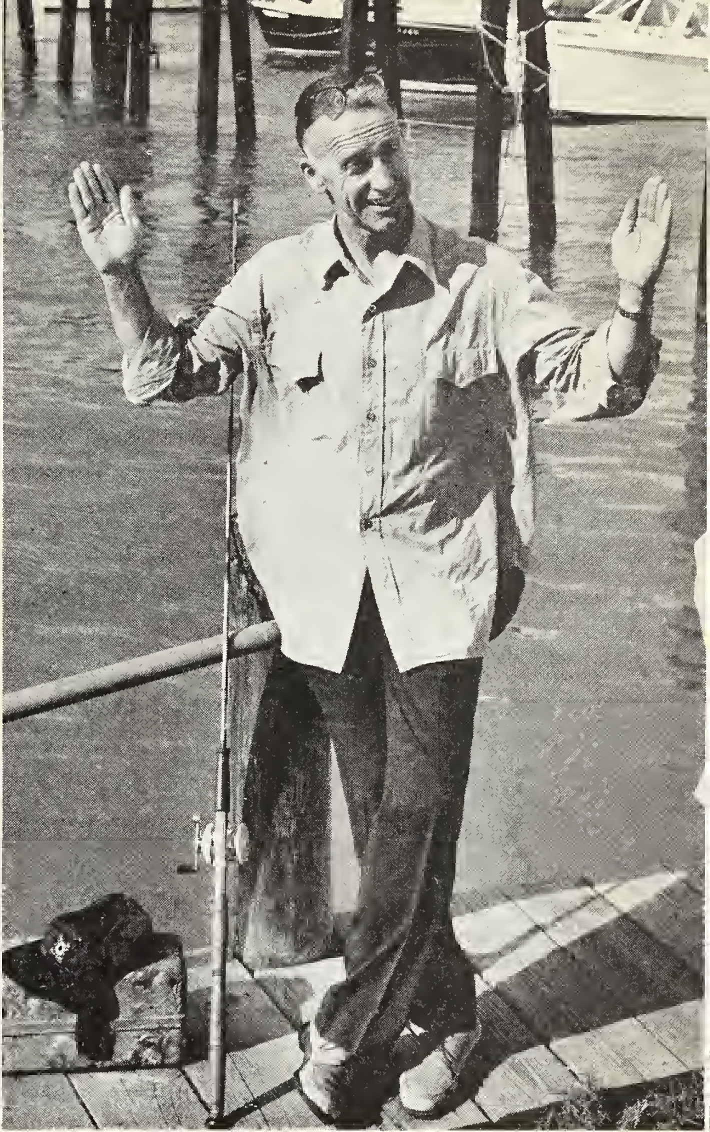
Speaking at a scientific session of the American Medical Association's 116th Annual Convention, John T. Connell, M.D., said he had evidence to indicate that:

(1) The initial or "priming" exposure to pollen at the beginning of hay fever season takes place only in the nose; it is not a systemic immunologic response as sometimes supposed. When one nostril of a patient is "primed" with pollen every day for five days, while the other nostril is closed, hay fever symptoms develop in the "primed" but usually not the unprimed side of the nose.

(2) The priming effect is reversible; when a patient is exposed to pollen in the laboratory every day for five days, in decreasing doses, a very small amount of pollen on the fifth day is capable of eliciting severe hay fever symptoms. After two more days without pollen exposure, however, even a large pollen dose is relatively innocuous, indicating that nasal reactivity has lapsed. The reversibility of nasal reactivity appears to be related to the duration of exposure to pollen; thus, in patients exposed to environmental ragweed pollen every day during the ragweed season, the reversal of the priming effect requires three to six weeks.

(3) The priming effect is not specific for any one kind of pollen; when a patient's nose is primed with one type of pollen, it becomes hyper-reactive to all other airborne antigens to which the patient is allergic.





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References: 1. Batterman, R. C., and Grossman, A. J.: Fed. Proc. *14*:316, 1955. 2. Goodman, L. S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Company, 1965, p. 331. 3. Roth, J. L. A., *et al.*: Gastroenterology *44*:146, 1963. 4. Conney, A. H., and Burns, J. J.: J. Pharmacol. Exp. Ther. *128*:340, 1960. 5. Settel, E.: Clin. Med. *6*:1373, 1959. 6. Berman, H. H., *et al.*: Dis. Nerv. Syst. *25*:430, 1964. 7. Darienzo, C.: Ibid., *27*:189, 1966.

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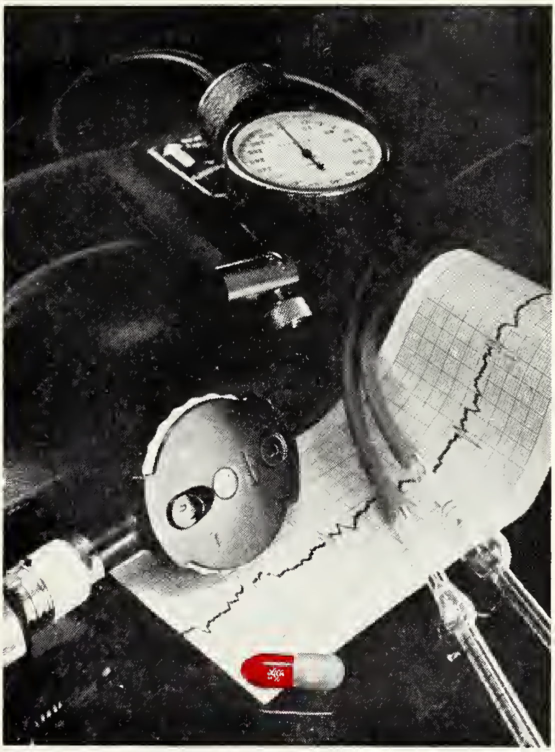

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editorials

Interrelationship Between Gallbladder Disease And The Electrocardiogram

Kaufman and Lubera[1] have recently seen three patients with chronic gallbladder disease and cholelithiasis whose electrocardiographic patterns showed marked inversion of the T wave in the electrocardiogram which we recognize as evidence of extensive myocardial damage or even acute myocardial infarction. In the presence of gallbladder disease it is important that such ECG changes be not interpreted as conclusive evidence of true myocardial ischemia. It is important that a more astute clinical judgment be made in the presence of gallbladder disease to determine whether the patient who requires surgery frequently, is simultaneously suffering from biliary tract disease and or serious coronary heart disease.

It has been known since 1935 that patients with angina pectoris and gallbladder disease had abnormal ECG patterns consisting mostly of inverted or flat T waves which become upright after cholecystectomy. This finding has been amply confirmed since by many workers. Obviously the ECG changes are the result of reflex influences upon the heart from the gallbladder and biliary system. This has led to numerous experiments on animals to determine its mechanism.

Animal experiments have shown that distension of the gallbladder, biliary tree and even the stomach results in a decrease in coronary blood flow. The mechanism appears to be a reflex vasoconstriction of the coronary arteries initiated by the distended or diseased gallbladder and mediated by way of the vagus nerve. If the vagus is sectioned or its action paralyzed by atropine, the reduction in coronary blood flow is abolished. Other studies have shown that ECG changes will occur in this situation, but only after some abnormality of coronary flow has been produced. All these studies have been confirmed also in experiments on humans with biliary tract disease by distension of the gallbladder and common bile duct. Nonspecific T wave changes have been produced, occasional disturbances of heart rate and even angina when the common bile duct was distended through a T tube.

The coexistence of gallbladder disease and coronary heart disease in the same patient has been extensively studied as has also the surgical management of this combination. Some patients with gallbladder disease have chest pains and severe ECG changes which may make the physician hesitant to advise operation, but if the changes are due to reflex influences upon the coronary circulation their disappearance can be demonstrated if vagal influences are abolished by atropine.

The report by Kaufman and Lubera shows that three out of four patients with gallbladder disease and marked T wave inversion developed this pattern through reflex influences. To establish whether or not coronary artery spasm had any role in the genesis of this serious electrocardiographic abnormality, they gave their patients 2 mg. atropine. An ECG was taken before and forty-five minutes after an intramuscular injection of atropine sulphate. Three showed marked improvement in the T wave abnormality. The test appears to be diagnostically significant because the ECG reverted to its original abnormal pattern after the effects of atropine had disappeared. Furthermore, following cholecystectomy the T wave rapidly and permanently reverted toward normal. By way of contrast a fourth case was a patient with myocardial ischemia due to coronary artery disease whose ECG tracings did not improve forty-five minutes after atropine administration.

It is obvious that a marked abnormality of T wave in a patient with gallbladder disease need not discourage a surgeon from doing essential biliary surgery. It should not be too difficult to eliminate

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THE CONQUEST OF YELLOW FEVER

METHODS of controlling and preventing yellow fever resulted from investigations conducted in 1900 at Camp Lazear, Cuba, by a United States Army Commission led by Major Walter Reed (1851-1902). This research proved conclusively that mosquitoes carry the yellow fever virus from person to person. First volunteer patient to be infected by mosquito bites was Private John Kissinger. Examining physicians were Major W. C. Gorgas, Havana sanitation officer; Dr. A. Agramonte, pathologist; Dr. Carlos J. Finlay, chairman of the cooperating Cuban Yellow Fever Commission and first man to point to the possible infective role of mosquitoes; Dr. James Carroll, bacteriologist; and Dr. Reed, commission chairman.

the reflex effects upon the heart by an atropine test and a repeat ECG forty-five minutes later. In this test it will be the doctor that determines the state of the patient's heart and not the first electrocardiogram.

Atropine sulphate will not only block many of the effects of vagal influences known to be initiated in the gallbladder and other abdominal viscera. A 2 mg. dose may cause dryness of the mouth, dilatation of the pupil and even some temporary blurring of vision. Urinary retention and exacerbation of glaucoma and even temporary psychoses are known to occur with the use of atropine. Although these were not found to be problems in Kaufman's patients they must be borne in mind by the physician who orders the post-atropine electrocardiogram and who wishes to establish the importance of reflex vagal influences upon the coronary circulation in those patients with gallbladder disease who urgently need surgery. It certainly also points up the value of anticholinergics as a part of the general routine in such patients even before surgery is contemplated.

We have for a long time known about the vagal supply to the heart and upper abdominal viscera. The gallbladder as well as the heart receives fibers from the right vagus and also from the splanchinic nerves derived from the sixth thoracic through the first lumbar segments along with the celiac plexus. The reflex vagal effects upon the heart are also long established; slowing, shifting pacemaker and at times coronary vasoconstriction. A return to basic physiological and anatomical knowledge is always fruitful. In the case of the coexistence of gallbladder and coronary heart disease, the physician can exercise more astute clinical judgment by recalling the nervous interconnections between these two systems.

L.H.N.

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Effect Of Graded Exercise On Fibrinolytic Activity

We are now in a mood to finally accept the value of exercise as a means of reducing the work of the heart in a patient suffering from coronary artery disease. It has also been shown that exercise is valuable in patients suffering from obstructive lung disease, provided the exercise is built up slowly and the conditioning continues. The manner in which muscular exercise helps pulmonary and coronary artery disease patients is by reducing the work of the heart as the muscles become more efficient metabolic machines capable of doing more work with the same amount of oxygen. An unanswered question is whether muscular exercise reduces the tendency to thrombus formation in arteries and thereby perhaps contributing to a better prognosis in arterial disease.

It is known that on the venous side, the red thrombus forms if stasis occurs and if there is also a hypercoagulable state of the blood. The whole tendency in recent years therefore has been to avoid stasis and try to eliminate as much as possible the factors causing hypercoagulability. As a consequence of this reasoning, early ambulation, post-operative and in the puerperium has greatly reduced the incidence of fatal embolism. There are still patients, however, that have to be in bed for a long time and patients with limbs long inactive in casts and it is worth considering whether other limbs that can be exercised can in some way contribute to blood fluidity in the inactive part. In short, if the legs must be inactive, can arm exercise contribute to blood fluidity and if arms must be inactive can leg exercise prevent the formation of a red thrombus in the arms.

It has been known for almost twenty years that exercise increases plasma fibrinolysis and many authors have considered that this increased fibrinolytic activity in strenuous exercise was due to a raised level of plasminogen activator. Menon et al.[1] studies fifty-eight university athletes for fibrinolytic activity after strenuous exercise such as football, rugby, squash and hockey both in men and women. Blood samples were taken before the game and after the game which lasted from thirty to ninety minutes. Graded exercise was similarly studied in ten young people in good health but not in athletic training. The untrained subjects were given a two step test, and blood samples were drawn before, after thirty minutes and sixty minutes after. The total exercise period lasted eight minutes.

The mean lysis time before the game in trained athletes was 248 minutes and after the game 87 minutes. The results were not altered by a cold shower. In the ten volunteers the initial lysis time was much longer than it was in the trained athlete, being 429 minutes, but after exercise it had declined to 290 minutes. The effects of exercise in both groups lasted for over one hour. These results confirmed earlier reports that increased fibrinolytic activity follows both moderate and strenuous exercise. The results are believed to be due to an

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excess of plasminogen activator presumably liberated by the venous endothelium for the most part. However, the factor in exercise that causes this liberation is not yet known.

The first question that arises is whether temperature plays a role in liberation of the plasminogen activator. We know that severe exercise raises body temperature. However, cooling the athlete off after the exercise did not reduce the resulting fibrinolytic activity. Bedrak in 1965 studied Alsatian dogs after muscular exercise in a hot environment and found enhanced fibrinolytic activity, which was not quite so striking if the dogs were first acclimatized. However, they still retained their post-exercise increase in fibrinolytic activity.

A second question is whether the plasminogen activator released after muscular exercise might be the result of adrenalin liberation. This question is still unanswered. It is true that the trained athletes all had a higher fibrinolytic activity than the untrained subjects. In the untrained subjects the exercise was light and the effects persisted longer than adrenalin acts. Nevertheless, adrenalin could have caused the increase in plasminogen activator which may have a slower disposal time than the original adrenalin.

The question of whether enhanced fibrinolytic activity induced by muscular exercise is of any value in relation to the development of atherosclerosis is a topic which has been widely discussed. Patients who have enhanced fibrinolytic activity such as those with hepatic cirrhosis and other forms of non-obstructive hepatic disease do have a reduced incidence of myocardial infarction. Similarly lack of physical activity has been suggested as a factor in the etiology of coronary artery disease and in particular myocardial infarction.

It is generally agreed that enhanced fibrinolytic activity is beneficial to the human organism. Menon's results are useful in a practical way because his findings suggest that while strenuous exercise may produce excellent results against thrombus formation, even quite moderate exercise may cause an appreciable and quite prolonged effect in increasing fibrinolytic activity and presumably operating against red thrombus formation.

It is important to realize that exercise of an endangered quiescent part is not necessary. For instance a person with a leg in plaster might benefit from exercise of the arms several times a day and thereby reduce the risk of a thromboembolism. Obviously the fibrinolytic mechanism in venous thrombosis is more important than it is in arterial thrombosis where platelets form a white thrombus through factors unrelated to fibrin deposition. What is important about Menon's results is that modest exercise can raise fibrinolytic activity of the blood and operate against red thrombus formation anywhere in the venous system.

L.H.N.

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Phagocytosis, The Central Mechanism In Fever Production

In man, fever is a common manifestation of many different diseases, bacterial, fungal and viral infections, hypersensitivity reactions, both immediate and delayed, to antigens of both microbial and nonmicrobial origin, to tumors such as those of the kidney, malignant lymphomas and others. It would be satisfying to the mind of man if we could discover some fundamental mechanism which is stimulated by all these diverse conditions to produce fever. The first idea that a specific pyrogen endogenously produced by the rabbit polymorphonuclear leucocyte is responsible for fever was reported nineteen years ago by Professor Paul Beeson.[1] His report was viewed with some incredulity at the time. The experimental model he used was to inject bacterial endotoxin in rabbits. It was cleared from the blood stream in a few minutes, was taken up by granulocytes and the granulocyte released an endogenous pyrogen. The pyrogen seemed to act directly on the hypothalamic thermal center producing fever.

Today the granulocytic factor Beeson discovered is believed to have a central role in the pathogenesis of most fevers. The same relation between circulating endogenous pyrogen and fever has since been established in other experimental models. These involve the production of acute bacterial infections, the injection of certain viruses or whole bacteria into normal rabbits and injection of bacterial antigens for example tuberculin in sensitized rabbits. The mechanism of fever production in all these models is the same, phagocytosis of an antigen by the granulocyte, then production and liberation of a pyrogen which then in turn acts on the hypothalamic thermal centers to produce fever.

Further confirmation of the central role of the phagocyte in the pyrogen production in these diverse conditions comes from in vitro studies. It has been possible to produce endogenous pyrogen merely by interaction of the granulocyte with the injected agent in normal serum at 37° C. The agent can be endotoxin, virus or bacteria. In the bacterial system, the cells first phagocytize the organism and then release the pyrogen to the supernatant fluid. Somehow the release process is trig-

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gered first by phagocytosis. In fact if one blocks phagocytosis by a chemical inhibitor such as sodium fluoride, then no pyrogen is released. We can thus say that the pyrogen produced by granulocytes appears to be the principle "messenger" molecule in a wide variety of experimental fevers, and there is reason to believe that it plays the same role in many human fevers.

What can be the explanation for natural fevers in those patients with agranulocytosis who have insufficient granulocytes for significant pyrogen production? What about fevers in patients having other diseases in which mononuclear cells rather than granulocytes dominate the pathologic lesions? It is in this connection that Bodel and Atkins report[2] is of particular significance. Is it possible that human cells other than the granulocyte are also capable of pyrogen production and what may these cells be? If the fundamental principle of pyrogen production depends first upon phagocytosis of an antigen, then cells capable of phagocytosis other than the granulocyte may also produce pyrogen when insufficient granulocytes are present.

Bodel and Atkins thought that the monocyte which is also capable of phagocytosis may be a pyrogen producer. They studied six patients, three with leukemia and three with chronic neutropenia. They prepared leucocyte fractions from normal blood as well as the six cases and found that monocytes can also release pyrogen after stimulation by phagocytosis. They carefully considered whether in their six patients the few granulocytes present could produce enough pyrogen and correctly concluded that it had to be the phagocytosis by the monocytes which alone could explain the large amount of pyrogen liberated.

Even though the granulocyte has an important role in endotoxin and other fevers it may not be essential for this or other types of fever. Bodel and Atkins studies reveal that phagocytosis appears to activate mononuclear cells not merely in the blood stream but in the lung, lymph node, spleen, whereas tuberculin seems to release pyrogen only from the lung macrophages.

In patients fever is a common manifestation of many different diseases. Are these differences in both the stimuli and the pathways of pyrogen production due to corresponding differences in onset and duration of the fever? For example the temperature in bacteremia or endotoxemia may be reflecting prompt and relatively brief pyrogen production activated by the granulocyte. Perhaps the prolonged and sustained fever frequently observed in diseases such as malignant lymphoma, tuberculosis and agranulocytosis might result from activation of mononuclear cells in tissues such as the lungs, lymph nodes and spleen.

The particular type of stimulus used in Bodel and Atkins experiments to demonstrate the capacity for pyrogen production by blood monocytes is an uncommon one clinically. Perhaps viral infections, hypersensitivity phenomena, or even endogenous metabolic alterations in the cell will prove to be more common activators to induce pyrogen production. It is obvious however that to obtain a better understanding of various types of fever it will be necessary to study such factors further and also the susceptibility of different cell types in their ability to produce pyrogens.[3]

However, we already have enough information to see the grand design in nature to produce fever. The mononuclear cells as well as the granulocytes are capable of generating endogenous pyrogen especially in those diseases in which the granulocyte is not prominent in the pathologic lesions. It offers also a theory that "tissue" pyrogen may come from tissue macrophages rather than from parenchymal cells themselves.

L.H.N.

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Factors In The Production Of Digitalis Toxicity And Their Management

We are seeing more cases of digitalis toxicity because of our success in treating edema of congestive heart failure with diuretic drugs. The latter result in both sodium and potassium depletion in whose presence digitalis therapy may be associated with arrhythmias. At this point we need to make a distinction between digitalis toxicity due to electrolyte depletion and that due to overdosage. In the presence of an associated hypokalemia, digitalis toxicity can occur at an exceptionally low dose. Nevertheless, digitalis must be withdrawn and even though the toxicity regresses, the body K. should be repleted and only then can digitalis be re-instituted at the previously effective dose.

There is, at present, no specific antidote for digitalis excess that counteracts all of the physiologic effects of digitalis overdosage without introducing effects of its own. When energetic treatment of digitalis intoxication becomes necessary, then drugs which counteract one or another of the actions of digitalis must be used but the choice of the agent depends on the particular manifestation of digitalis poisoning which is most hazardous to the patient. Obviously withdrawal of digitalis as soon as toxicity is detected is always in order. This is the reason why nurses must be trained to understand the evidences of toxicity and immediately report them to the doctor. It is also a good reason for alerting the ambulatory patient to report to his physician the first sign of frontal headache, anorexia and "palpitation."

Restoration of normal function can be expected within hours to days depending on the glycoside used, if the digitalis has been completely withdrawn rather than reduced in dosage. Because of the frequency of electrolyte imbalances that occur after operations on the heart and after vigorous treatment for heart failure there has been a tendency to use digitalis preparations that are excreted rapidly which permits an easier method of overcoming digitalis toxicity should it develop.

More urgent treatment that mere discontinuance of digitalis becomes necessary when toxicity results from arrhythmias that interfere with cardiac function. These are roughly, sinus bradycardia or a–v block and the tachycardias. In the presence of a–v block there is no available effective drug. Administration of K in this situation may worsen the block or slow the ventricular rate because of the direct depressant effect of this ion. Isoproterenol often effective in improving cardiac rate in cases of heart block from other causes should not be used because of its propensity to produce severe arrhythmias in the presence of digitalis toxicity. It is an adrenergic drug which makes the myocardium irritable. The treatment of choice then for heart block or marked sinus bradycardia due to digitalis is the temporary introduction of an endocardial catheter pacemaker with control of the heart rate by electrical stimulation.

The treatment of toxic arrhythmias with rapid heart rates is much less satisfactory. However, since the cause of many of these tachycardias result from alteration of the cell membrane that encourages K exit from the myocardial cell, the need here is to "drive" K back into the cell and this requires administration of KCl intravenously in doses of 20-40 mEq. given over a period of one to two hours. If the situation is less pressing, K can be given orally as an initial dose of 4 grams KCl in solution followed by 2 grams every four hours until the arrhythmia is controlled. This has proved most satisfactory in the treatment of atrial tachycardia with block.

Unfortunately it is inconsistently effective with other rhythms such as ventricular tachycardia and valuable time may be lost during such treatment. Several methods have been proposed such as reducing the calcium concentration with EDTA to allow more pores in the cell membrane for K entry. But this and the use of Ryanodine, a natural alkaloid insecticide, have not been found effective. Neither has sodium citrate which can terminate the tachycardia but not prevent its recurrence a few minutes later.

In treating ventricular tachycardia not due to digitalis toxicity, the standard procedures have been cardiac depressant drugs such as quinidine, procainamide and in atrial tachycardia—digitalis. Furthermore, synchronized precordial shock has also been effective in tachycardias not due to digitalis toxicity. However, this last method, countershock, is not an acceptable treatment for tachycardias caused by digitalis toxicity. Although occasional prompt and permanent remission of digitalis induced tachycardia have been reported without side effects after electrical countershock, it has also been shown that shock is less likely to revert tachycardia due to digitalis than tachycardia due to other causes and that the tachycardia is more likely to recur rapidly. In fact the incidence of ventricular fibrillation is greatly increased as a complication of shock treatment in these situations. For this reason it is generally agreed that synchronized precordial shock is contraindicated in digitalis toxicity. Another electrical treatment paired-pulse stimulation has had little clinical trial and still remains in the experimental laboratory.

Quinidine and procaine amide or lidocaine will be effective in most ventricular tachycardias, however in the presence of digitalis intoxication one must expect a higher incidence of ventricular fibrillation than would otherwise be the case. Nevertheless they presently are the drugs of choice for life threatening tachycardias due to digitalis especially when the effect of K administration might be too slow and unpredictable. Intravenous procaine or lidocaine in doses of 100 mg. per minute are used until the tachycardia is terminated or hypotension or new arrhythmias occur. It may be continued until a dose of 2 grams is reached.

Since ventricular tachycardias are the result of the interaction of a toxic agent, in this case digitalis and beta-adrenergic stimulation[2] it is reasonable to expect that a beta-adrenergic blocking agent should be an important procedure in the termination of ventricular tachycardia due to digitalis toxicity. Such a drug propranolol is now undergoing intensive study in the treatment of digitalis intoxication.[3] Preliminary reports suggest that this agent is indeed effective in the control of arrhythmias due to digitalis. It also increased a-v conduction and can slow the ventricular rate when digitalis produces atrial fibrillation with a rapid ventricular rate.

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cardiac reserve may worsen incipient or existing congestive heart failure. For this reason further clinical study of propranolol is necessary. It, however, seems to be possible that this drug may turn out to be the best treatment available for tachycardia due to digitalis intoxication.

It is comforting to know that physiologic principles in the genesis of cardiac disturbances caused by digitalis permits us to apply rational measures in their management. Basic science is practical medicine and clinical practice is truly basic science.

L.H.N.

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Personal Health And Individual Responsibility

There is a widespread expectation that medicine can reduce suffering, conquer disease and ensure a better life free from physical and mental illness. This is only reasonable in the light of the explosion of biomedical knowledge and increased information which is potentially pertinent to the physician in his treatment of the sick and "well" individual. However, some people still carry copper bands to cure arthritis and eat potatoes to ward off the "Flu." Myths such as these are not confined to the stupid or uneducated and are harmless as compared with the prevalent myth that the responsibilty for the individual's health lies elsewhere than with the individual himself.

Moses was the first public health officer, not because he laid down a sanitary code for communities, their water, their air and their garbage, but because he directed specific prohibitions at each individual how to prevent disease. As far back as Hippocrates time, 400 B.C., two classes of disease were recognized, those due to external causes and those due to personal causes such as irregular food habits, exercise and other habits of the individual. These admonitions have not been fully heeded nor have they taken root.

The laws to enforce public health measures and the agencies set up with power and authority to enforce them are realistic, practical and when carried out protect the individual in society from external causes of disease. There are, however, obvious limits to their effectiveness in improving personal habits of each individual. When a doctor prescribes personal preventive measures for the individual patient there are serious blocks and limits to their compliance. Most people are more concerned with the problems at hand than with those in the future so that the self-discipline required to prevent disease can be sadly lacking. A person who does not discharge his responsibilities to society, family or friend earns penalties, scorn and criticism. An individual who fails to discharge his responsibilities to himself is usually ignored.

Is a person entitled to good health? The whole philosophy of our society says yes. The whole direction of biomedical advance says yes. Every individual says yes, but to what degree does he realize what he has to do to justify this entitlement? Half of knowing what you want, is knowing what you have to give up to get it. Now that medical science has developed adequate therapy for so many diseases one would expect people to exercise greater restraint and self-discipline, especially in respect to personal habits that have been shown to have harmful effects.

There is, however, developing a backlash. Instead of encouraging restraint and a degree of self-denial, a false belief is growing up that medical science will be able to cure everything. An attitude of this kind has led a large number in our society into carelessness, self-indulgence, excesses and self-detrimental acts all accompanied by a variety of rationalizations. We need not fear venereal disease, it is curable. Why worry about illegitimate pregnancy, there is the pill. Why not smoke, so I'll live shorter but enjoy it and besides by the time I'll get cancer it will be curable. There are so many parties but I'll be careful from now on, etc. Clearly it is necessary for the medical profession to put the facts squarely before the public so that we cannot be accused of inadequately practicing preventive medicine. Among the factors essential to the people's health are—not least, "wise, sensible conduct of the individual and his acceptance of personal responsibility."

In the Apocalypse war's evils are depicted as Conquest, Slaughter, Famine and Death. The four horsemen of the Apocalypse in peacetime are Accidents, Alcoholism, Smoking and Obesity. Accidents are the commonest cause of death in the young. Why in the young—because they lack individual responsibility to themselves and others which older people have already learned. Then there is accidental poisoning mostly among children. Medicine prescribed or purchased for other members of the family are responsible for more than half of the poisonings, despite direct warning to parents, and continued and steady publicity about such dangers.

Alcohol consumption is increasing over and above the population increase. In Canada with a population one tenth of ours, there are an estimated 400,000 alcoholics.[1] In this country at least

2,500,000 and another 2,500,000 with various impairments. What this means in self destruction, misery, poverty and injury to others needs no elaboration. Regardless of whether or not alcoholism is labelled a disease there is a behavioral component capable of being controlled through a form of self-discipline as witness Alcoholics Anonymous.

There is a causal relationship between smoking and disease despite irresponsible statements to the controversy. Government agencies, medical organizations, individual doctors and health personnel are engaged, though feebly, in an educational program against smoking. Despite this the sale of cigarettes increased about 15 per cent in the last six years. Obesity causes ill health. Excepting the obesity caused by disease, it is a self-induced affliction, a perfect example of the abandonment of individual responsibility. The horsemen of the Apocalypse ride on leaving death and disease in their wake.

Preventive medicine cannot be effective unless the patient understands, cooperates and accepts the necessary restraints of his personal liberties. Henry M. Wriston, President Emeritus of Brown University has stated[2] that "Democracy is the political aspect of the assertion of the supreme importance of the individual." This kind of democracy demands "Development of the individual physically, mentally and morally." . . . "Central to this idea are the stimulation and the discipline of the individual." There is no such thing as "Mass Education"—education is a wholly individual process; the life of the mind . . . remains a private life responsibility, a private responsibility.

"Doctor" means a learned man, a "teacher." It is only logical that Doctors should take the lead in demanding a complete re-examination of the present health education of our children. This education must be established in early childhood not after habits and indifference to health are already well established. The health-giving and life saving truth is that preservation and maintenance of personal health is an individual responsibility. It calls for self-discipline. It calls not only for knowledge but for the desire, the motive in each individual to promote his own health.

There is no doubt of the gaps that exist in the teaching of preventive health measures in our schools. Demands exist for sex education but this is merely a small part of health education and not as important as mental health about which so little is taught in our schools. Formal health education starts at about ten to eleven years of age, too late to teach good personal habits, too late to emphasize the lifetime self-discipline needed to preserve health.

A re-examination of our health education system is in order. It is not the responsibility of the doctor alone but of all citizens. During this re-examination the present system should be evaluated, effectiveness of each system assessed and constant re-evaluation to improve teaching should be built into any system of teaching health.

The great myth that we needn't worry about future health, we can leave it to medical science will persist unless this is done. Laws alone or knowledge alone will fail in efforts to affect personal habits as witness Prohibition, and the futile gambling laws. We, of course, cannot be sure that the great myth can be destroyed by education. But it must be successfully counteracted since the health of the people, just as their civilization will "be measured by the extent of their obedience to the unenforceable"—to their own self-discipline.

L.H.N.

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Experiments In Medical Education: A New Curriculum At Sherbrooke

It is nothing short of a miracle that modern methods of instruction have not entirely strangled the holy curiosity of inquiry.—Albert Einstein.

There is widespread recognition that medicine must evolve new patterns in both medical and post graduate education. The patterns will require that we deepen our roots in science and at the same time that we broaden our scope of service to mankind. The hope for the future requires that we must reconsider the curriculum in our medical schools and proceed with bold innovations in premedical and post-graduate education as well. The recognition that no individual can learn all the information in the biological sciences and that the Doctor of Medicine must be prepared for a diversity of roles requires an increased flexibility in medical school curriculum.

We all know that the medical facts of tomorrow will be different from those of today and this should reduce our compulsiveness with which we stuff our students with today's "facts." It has been estimated that the half life of present facts is about eight years and therefore when a postgraduate doctor is ready to take his Board Examinations eight years after his entry into a medical school, much of what he has learned as "facts" will have to be replaced. It would be better, therefore, if we cultivate habits of independent thinking and scholarship which will ensure continuing assimilation of new knowledge after graduation.

Undoubtedly different schools will adopt different ways of meeting the need for greater flexibility in the medical curriculum, to emphasize independent thinking and scholarship rather than rote memorization. Changes in curriculum can at best only facilitate the learning experience. The essence of education, therefore, is to bring together the intelligent motivated student with the teacher. The teacher's role is to reduce the barrier between him and his student and with knowledge and enthusiasm for his subject to inspire his student to seek knowledge and explanations for that knowledge.

A new medical school in Sherbrooke, Quebec has just announced its approach to educating the future Doctor of Medicine. Dean Beauregard explains the four major objectives of the new school as education with emphasis on the learning process, research in three major fields of endeavor, basic, clinical and medico-social sciences and optimum patient care and service to society. All these trials will have to be of a dynamic nature to be revised and reassessed constantly and critically by both professors and students.

During the first year there will be four periods of two months each, cell biology, normal tissues, abnormal tissues, and then two systems closely related to tissues, skin and blood. Cell biology is to be studied with the help of cytologists, embryologists, biochemists, biomathematicians, geneticists and neurobiologists.

Normal tissues are to be studied under the guidance of histologists, biochemists, biophysicists and physiologists. Abnormal tissues will be studied with the help of biophysicists, microbiologists, pathologists and pharmacologists. In the fourth period of the first year more specific clinical problems are introduced through the study of dermatology and hematology, which will require the collaboration of geneticists, clinical laboratory specialists, immunologists, pharmacologists and dermatologists.

Throughout the first year as the student learns about the various components of man, that is to say, his cells, tissues, organs, he will likewise delve at another level into the various components of society, man and his development in health and disease, repercussions of health and disease upon the family, the community and society. The point is to make the student become aware of his role in society as well as his responsibility in the management of individual patients.

During the second year there will be five blocks, neurolocomotor, cardiovascularrenal, respiratory, gastro-intestinal, endocrines, including obstetrics and gynecology. Here again the professors will be picked from both clinical and fundamental disciplines. This should make students more aware of the importance of basic science in the management of patients.

Obviously such objectives can only be attained through new methods of approach to learning. Because of rapid obsolescence in "facts" the emphasis will be on attitudinal changes which can develop only slowly not only in the student but in the professor as well.

Motivation will be improved by introducing the student to patients in the course of the first year when they are studying genetics and embryology. The student will begin to take histories and examine the patients. Autopsies will be brought into play to assist the student in learning the anatomy of internal organs. Hopefully students will be led to raise questions and recognize problems of applied pathology and will write out reports on the history, physical examination, laboratory results and evolution during the patient's hospital stay in relation to the gross and microscopic findings. In this way he may acquire the habit of problem solving.

There will be tutorial sessions between students and professors, seminars and comprehensive examinations whose aim primarily is to allow the student to evaluate his progress and the professor to evaluate his own success or failure in the role of teacher. The examinations are integrated because members of at least two disciplines are collaborating in the courses offered.

The last two years will be spent in the university hospital or clinical teaching units in specified clerkships. Here students will learn to use the problem solving approach to each patient. This procedure would include in the work up a return to all basic sciences necessary to the solutions of the problems of diagnosis and management.

We all hope that the innovations, faculty enthusiasm and methods of encouraging learning at Sherbrooke will bring about the positive attitude wished for by Albert Einstein who wrote "it is nothing short of a miracle that modern methods of instruction have not entirely strangled the holy curiosity of inquiry."

L.H.N.

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Bioamines And Emotion: II. Catecholamine Hypothesis Of Affective Disorders

A significant clarification of our understanding of the possible relationship of the biogenic amines to affective states has come from studies of the changes in metabolism of brain monamines produced by clinically active psychotropic drugs.[1] Reserpine has been reported to produce severe depression of mood in some patients especially those with hypertension treated with relatively large doses. The action is reversible when the drug is stopped. The question is how close to naturally occurring depressive disorders is this one produced pharmacologically, and what does reserpine do to bioamines in the brain?

In experimental animals reserpine interferes with neural binding of the catecholamines and serotonin in which they become inactivated and their stores depleted. As the brain levels of these amines decrease, the animals enter into a state of sedation analogous to depression in man. Once the brain recovers its capacity to synthesize norepinephrin, normal motor behavior of the reserpine sedated animal returns. The hypothesis suggests itself that reserpine induced depression is related to impairment of the binding of monoamines. Any chemical which can pass the blood brain barrier and be converted to norepinephrin should therefore restore gross behavior of the animal to normal. The role of serotonin in the reserpine syndrome seems to be similar to that of catecholamine, for its production causes central excitation and its depletion contributes to depression.

There are, however, drugs that can reduce serotonin content of the brain to 10 per cent without changing the norepinephrin content, but sedation is not observed. Apparently there must also occur depletion of norepinephrin in the brain to achieve depression. There are also drugs that inhibit brain synthesis of these amines—monoamine oxidase (MAO) inhibitors. Such drugs have been reported to be effective in the treatment of depression. What has not as yet been solved is the relative clinical effectiveness of some of the MAO inhibitors and whether there are specific subgroups of depressed patients for whom these drugs are indicated.

The question, of course, is wether there is a correlation between behavioral excitation and increased concentration of a specific amine. By using various inhibitors, doses, and animal species it can be shown that behavioral excitation is temporally related with increase in levels of norepinephrin but not of serotonin. Does the excitation which follows MAO inhibitors arise from a spillover of free norepinephrin on to receptor sites? This is probably a justified theory in view of the fact one can antagonize reserpine induced depression by prior treatment with an MAO inhibitor.

Imipramine and other tricyclic antidepressants have been found to be the most clinically effective of the antidepressant drugs. This drug seems to potentiate the response to sympathetic nerve stimulation and also the peripheral effects of administered norepinephrin in man. Prior treatment with imipramine can prevent reserpine induced sedation in animals. It would seem, therefore, that imipramine exerts its antidepressant action through potentiation of catecholamines at adrenergic receptor sites in the brain.

Amphetamine is a short acting sympathomimetic psychic stimulant but its results in the treatment of depression are variable. How it acts is still speculative. It could act by the release of physiologically active norepinephrin from nerve cells and also by blocking inactivation of norepinephrin by cellular re-uptake. It may exert a direct effect at receptor sites. Lithium salts have been used in hypomania. Schildkraut and Kety think its action is probably the result of deamination of norepinephrin and its decrease at adrenergic receptor sites.

If depletion of norepinephrin is related to depression and its excess availability is associated with manic states, then precursors of norepinephrin that can pas the blood brain barrier should help to overcome depression. Conversely drugs that reduce availability of norepinephrin at binding sites in the brain should serve to overcome manic states. It is thinking of this type which has led a number of investigators to formulate the concept designated the Cathecholamine Hypothesis of Affective Disorders: that some if not all depressions may be associated with a relative deficiency of norepinephrin at functionally important adrenergic receptor sites in the brain, whereas elation may be associated with an excess of such amines.

Even though there appears to be a fairly consistant relationship between the effects of pharmacologic agents on norepinephrin metabolism and on affective states, confirmation of this hypothesis must ultimately depend on direct demonstration of the biochemical abnormality in the naturally occurring illness. Suppose such a demonstration of a biochemical abnormality could be demonstrated, would this necessarily imply a genetic or constitutional basis or could it also result from environmental psychological factors as well?

It is conceivable that specific genetic factors may be of importance in the etiology of some and possibly all depressions or manic states. It is equally conceivable that early experiences of the infant or child may cause enduring biochemical changes and that these may predispose some individuals to depressive states in adulthood. We already have parallels of this concept in the developing knowledge of the role of hormones in the organization of the nervous system (gonadal hormones, corticosteroids, thyroid).[2]

A final question is whether changes in the metabolism of the biogenic amines can alone account for the complex phenomena of normal or pathological affect? Schildkraut and Kety think this not likely. It is true that the effects of these amines at particular sites in the brain may be of crucial importance in the regulation of affect. Many other concomitant biochemical, physiological and psychological factors, may have to be inluded in any comprehensive formulation of the physiology of the affective states.

There must be many intricate environmental and psychological determinants of emotion whose importance cannot but be stressed. We know from personal experience, how easily affective states are induced by environmental events. What role cognitive factors which are derived from the individuals remote and immediate past experience play, will need particular exploration. Before we may expect to understand fully the relationship of the biogenic amines to emotional states, we obviously will need investigation in a wide variety of parameters. In other words, by a multifactorial approach.

L.H.N.

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The Korotkoff Sounds In Shock

There is no doubt that there is a resurgence of emphasis on the value of the stethoscope in diagnosis. The advent of surgery for congenital heart disease and rheumatic heart disease has enhanced the value of the stethoscope. Listening for abnormal sounds is no longer an academic exercise in diagnosis of formerly incurable lesions. It is an effort well rewarded by success.

The usefulness of auscultation has extended well beyond the chest, to include the neck, abdomen and extremities. Listening over the carotids is now a necessary feature since carotid artery lesions can cause intermittent or permanent cerebrovascular damage. Similarly we know that renovascular lesions are removable causes of some cases of hypertension and this has made it imperative to auscultate the flanks, loins and upper abdomen in every case of hypertension for the telltale murmur of renal artery obstruction. Occasionally a pancreatic tumor obstructing the splenic artery and a hepatoma obstructing the hepatic artery can also produce a murmur and this also directs our attention to auscultate over these abdominal organs.[1,2,3]

If the stethoscope is becoming a more useful tool than ever before, we must also recognize its limitations especially in auscultating for the blood pressure and pulse pressure in shock. Cohn[4] has previously pointed out that some patients will have the peripheral manifestations of shock and still have normal intraarterial pressure when there is markedly reduced or even absent cuff pressure and upper extremity pulses. It is important to recognize that low cuff pressure and upper extremity pressure do not necessarily indicate hypotension.

Cohn performed his studies by simultaneously recording intra-arterial and cuff pressures in patients with hypotension and shock. He also set up an experimental model in normal subjects to determine why it is that the Korotkoff sounds and arterial pulsations tend to disappear in shock. In the normal subjects he infused angiotensinase into the arm to raise the peripheral vascular resistance. At a certain point when the peripheral vascular resistance in the arm was sufficiently raised, the pulse and Korotkoff sounds disappeared. Of course raising the peripheral vascular resistance reduced the flow of blood through the arm and forearm and this was associated with marked diminution of the intensity of the Korotkoff sounds and obliteration of the pulse.

In the presence of experimental arteriolar constriction in the upper extremity, the diastolic runoff is of course slowed and a sharp pressure drop does not occur below the occluding cuff. The absence of a pressure drop would then prevent the jet flow which is necessary for the production of arterial sounds. In addition the experimental vasoconstriction produces increased arterial wall tension and this also might render the artery wall less likely to respond with audible vibrations.

It is worth recalling that the sounds created over the brachial artery when a cuff on the arm is inflated between systolic and diastolic pressure probably results from vibrations in the arterial wall set in motion by intermittent flow through the compressed segment.[5] The passage of a momentary jet of blood when the artery is forced open by the propagated pressure wave depends in part on a sharp arterial pressure gradient from above to below the occluding cuff. If there is absence of Korotkoff sounds then either insufficient flow has occurred through the compressed vessel or the vessel wall has been altered so that audible vibrations do not occur. Rodbard[6] has emphasized the role of blood flow in determining the intensity of the Korotkoff sounds.

It has been known for a long time that Korotkoff sounds may not be audible in some cases of shock. In Cohn's patients with shock, in those that had cool clammy skin and also a high peripheral vascular resistance, the blood pressure obtained by Korotkoff sounds below the cuff or by palpation of the artery greatly underestimated the arterial pressuer just as did the same phenomenon produced experimentally by vasoconstriction in normal subjects. The auscultatory pulse pressure was very narrow and yet when measured directly by a catheter in the artery the pulse pressure was actually not reduced.

Even though the brachial and radial pulses were often impalpable, in five patients with shock, femoral pulsations usually remained strong. Such observations make it unlikely that the disappearance of peripheral pulses in shock can be accounted for by diminished intra-arterial pulse pressures.

The pulse felt over a peripheral artery depends first on the pressure fluctuations within the vessel. Second it depends on the ability of the fingers to compress the vessel and to detect expansion with each pulse wave. In the presence of vasoconstriction a frequent compensatory mechanism in shock and especially if levarterenol is infused with the intent of raising arterial pressure, the smaller muscular arteries become less compressible. Finally there is diminished distensibility and a much reduced volume of blood advancing in the artery with each heart beat. This could produce normal intra-arterial pressure fluctuations with a diminished or even impalpable arterial pulse and certainly absent Korotkoff sounds.

The discrepancy between intra-arterial and cuff pressures in patients with shock may have important clinical implications. A false impression of hypotension by Korotkoff sounds and palpation can lead to treatment with vasocompressor drugs, produce actual hypertension and even acute heart failure. Evaluation of the strength of the femoral pulsations often gives valuable information about the level of arterial pressure in vasoconstricted patients. It is readily understood why infusion with Dextran 40 and the use of isoproterenol is coming to replace vasoconstrictor drugs in the treatment of shock.[7]

L.H.N.

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Depression From Infant-Mother Separation

Higher organisms that are not precocial do require parental care in order to develop normally. The relationship between infant and mother is thus crucial and the consequences of disruption of this relationship are momentous.

Engel[1] has described two basic response systems as available to an organism for dealing with mounting stress. One is an agitated phase, the "flight-fight" response pattern is one intended to effect a reunion with the mother if she is available. A second phase is strikingly similar to the syndrome of anaclitic depression also reported by Spitz in human infants separated from their mothers. This response pattern was termed by Engel "conservation-withdrawal" and involves inactivity . . . with withdrawal from the environment." It appears to conserve energy and avoid injury. If the human infant had greater development of locomotor ability he could perhaps be enabled to re-engage the environment actively on his own. But in the absence of locomotor activity serious and severe effects in human infants do follow separation from mothers for more than a brief period.[2,3]

Kaufman and Rosenbloom[4] have just described their results of a months separation of infant pigtail monkeys from their mothers. They found two striking effects of the months separation. Three of the four infant monkeys developed a severe depression and in all four there was a marked and long lasting intensification of the mother infant relationship after mother and infant were reunited. The physical separation of mother and infant was done outside the pen with a minimum of handling and trauma. The mother was placed in a separate location and the infant returned to the group. After four weeks the mother was returned to the group.

The reaction separation in three infants fell into three phases, agitation, depression, recovery. A fourth infant showed agitation and recovery without depression. During the agitation phase, there was pacing, searching, head movements, frequent trips to the doors and windows, sporadic but short lived bursts of erratic play, and brief movements to other members of the group. Cooing the plaintive distress call of the young macaque was frequent and there was also much self-directive activity such as sucking of digits, mouthing and handling other parts of the body including the genitals and for the first twenty four hours the infant did not sleep.

After this each infant sat hunched over almost rolled in a ball with head down between his legs. Movement was rare except when the infant was actively displaced. The movement which did occur appeared to be in slow motion, except at feeding time or in response to aggression. Play virtually ceased. The infant appeared disinterested in and disengaged from the environment.

Gradually the recovery started after five to six days with resumption of a more upright posture and resurgence of interest in the inanimate environment. Slow tentative exploration was then followed by attempts to interact with his social environment and then he began to play. But the depression though abating continued. Periods of depression alternated with periods of inanimate object ex-

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ploration and play. Movement increased in amount and tempo. Towards the end of the month the infant was alert and active a great deal of the time although he by no means behaved like a typical infant of that age.

When the mother was reintroduced to the group another dramatic change occurred. There was a tremendous reassertion of the dyadic relationship with marked increase in closeness. Clinging by the infant, protective enclosure by the mother and nipple contact all rose significantly in the month after reunion. Even in the third month after reunion this trend was still evident. This is striking in view of the fact that ordinarily for the age periods involved, these particular behaviors fall considerably. It is very significant also that maternal behavior which normally discourages dyadic cohesiveness at this age such as punitive deterence and nipple withdrawal appeared very rarely.

It would appear that the stages of reaction observed by Kaufman and Rosenbloom represent the successive efforts at adaptation noted above for the human infant. The striking similarity between the early stages of the reaction of separation of pigtail infants and the human infant suggests that the mediating central nervous system response systems may be common to both species. The recovery phase not seen in the human infant may be attributed in the monkey infant to his greater locomotor ability which enables him to re-engage the environment actively on his own. The human infant without developed locomotor ability cannot re-engage his environment and must remain in a phase of depression.

L.H.N.

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Polymyalgia Rheumatica And Blindness

Polymyalgia rheumatica is a term first suggested by Barber in 1957 for the syndrome of severe limb-girdle muscle aching and stiffness in elderly persons who also have strikingly elevated E.S.R. usually about 100 mm. by the Westergren method. There seems to be no evidence of inflammation in the muscles: the serum enzymes such as phosphocreatinekinase that often reflects muscle necrosis are normal. Muscle biopsy shows neither inflammatory cells nor changes in the fiber and the electromyogram is normal.

The syndome has been discussed extensively in Europe and Séze has published a comprehensive review.[1] Whether it is more common abroad or more frequently recognized there than in this country is still moot, although a number of reports indicate it is present here also and Davidson[2] has found fourteen cases at Mount Sinai in New York in the last two years and one case was reported in this Journal recently.

The syndrome has practical importance as in the two cases of blindness reported by Fessel and Pearson.[3] In the first place before the correct diagnosis is established patients are usually studied exhaustively for the presence of other diseases especially neoplasms that may be intracranial or have spread to the vertebra. This leads to tedious diagnostic studies that are almost always made but which might be avoided if the possibility of polymyalgia rheumatica were considered. In this case temporal artery biopsy would be made early and might reveal a giant cell arteritis. The second point is that the existence of a cranial arteritis carries a danger of sudden blindness which the physician may avert if forewarned.

It has been known for many years that the elderly who are the chief sufferers with polymyalgia rheumatica are also subject to a destructive vasculitis involving the aorta, its principal branches, and especially the cranial arteries. Like other vasculitides, temporal and cranial arteritis causes a remarkably varied clinical picture, but one of the more serious events is blindness. In addition aching muscles, pains and lameness about the shoulder girdle is a common manifestation. The question of course arises whether in such patients the symptoms of polymyalgia rheumatica are a result of the arteritis or whether both vasculitis and polymyalgia rheumatica coexist in the same patient.

From the nosologic point of view polymyalgia rheumatica could be a disease, sui generis, or a variant of giant cell arteritis or a mixture of various disorders one of which is giant cell arteritis. There have been a number of reports of polymyalgia rheumatica in which at a later date a few patients developed rheumatoid arthritis. The reports, however, because the patients had no visual disorders, did not reveal that temporal artery biopsy was done. There may, in fact, be no external evidence of temporal arteritis and yet the biopsy may at times be positive. Obviously in the absence of a biopsy in such patients it is not possible to say that polymyalgia rheumatica is a separate entity from giant cell arteritis.

There is a similarity between polymyalgia rheumatica and giant cell arteritis. In the first place a definite number of patients of polymyalgia rheu-

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matica do have giant cell arteritis and the incidence as Fessel and Pearson point out varies from seven out of nine, to seven out of fifteen to twelve out of twenty-one cases examined by different workers. Furthermore, in patients who have had biopsies of the temporal artery, thirteen were found positive out of seventy and in another series ten were found positive out of thirty patients diagnosed as having polymyalgia rheumatica.

If polymyalgia rheumatica is a variant of giant cell arteritis then one would think that it exists as a benign form also. Nevertheless a relatively high incidence of giant cell arteritis is present in polymyalgia rheumatica and may be the underlying disease in up to half of the patients. The matter is important because it is generally agreed that the severe complications of cranial arteritis especially blindness can be controlled and even prevented by corticosteroid therapy. The doses usually required, however, are large enough to subject the patient to many of the side effects of such agents and in the elderly, intercurrent infections or crippling osteoporosis.

It is clear that we must have a high index of suspicion for polymyalgia rheumatica in elderly patients who suffer from a syndrome of severe limb-girdle muscle aching and stiffness and who have a high E.R.S. Such patients require that a biopsy of the temporal artery be made and if arteritis is seen especially with giant cells, then steroids should be used in high doses—the equivalent of 40—6 mg. prednisone daily for twelve weeks, to reduce the incidence of blindness and the majority of visual complications which may appear within twelve weeks of the onset of general symptoms. After the initial treatment with large doses of steroids, the patient may require maintenance on low doses for a longer period to control the myalgia.

If polymyalgia rheumatica is not always due to a vasculitis, how can we recognize it as a separate entity without biopsy of the temporal arteries. There are even reports that in cranial arteritis even with extensive involvement, the temporal artery may be spared. Nevertheless much can be said in favor of routine biopsy of the temporal arteries in suspected cases of polymyalgia rheumatica to rule out cranial arteritis. This does not rule out the value of steriods but makes smaller doses advisable if giant cell arteritis is not revealed.

L.H.N.

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Biliobronchial Fistula. Report Of A Case

Gustaf E. Lindskog, M.D. and James M. Shannon, M.D.

Biliobronchial Fistula

Biliobronchial fistula is a rare condition characterized by a pathologic communication between the liver or extrahepatic biliary tract and the bronchial tree. The pathognomonic symptom, usually an unmistakable one, is the expectoration of bile or bile-stained sputum. The lesion is of infectious or traumatic origin, sometimes related to imperfect surgery.

According to Morton and Phillips (1928) amoebic abscess and echinococcus cyst of the liver are the principal causative lesions. However, in the present era and in this part of the world, pyogenic abscess of the liver or the sub-diaphragmatic spaces provides the usual exciting cause. Blockage of the common duct by stone, strictures, granulomas or, rarely, parasites leads to increased intrabiliary pressure, bile retention, ascending cholangitis, hepatic abscess or subdiaphragmatic peritonitis. When allowed to evolve without adequate medical and surgical treatment, an abscess may dissect through the substance of the diaphragm along lymphatic channels into an adherent lung or into the free pleural space. (This course may be precipitated by errors in surgical technique). The essential pathologic process is, in general, below the diaphragm and not above it. *Primary* suppurative disease of the lung and complicating pleural empyema almost never traverse the diaphragm to the peritoneal spaces inferiorly except in certain cases of tuberculosis or actinomycosis.

Morton and Phillips' review of the literature in 1928 revealed fifty cases of biliobronchial fistula, including one of their own experience. Other cases have been added sporadically since that time. Guy and Olack (1947) were able to collect a total of 64, six of which were clearly traumatic in origin. Considering the large number of military wounds which may involve the diaphragm and liver simultaneously it is remarkable that World War II and the Korean War have yielded few reported instances of biliobronchial fistula.

In penetrating wounds of the chest wall, diaphragm and liver especially when caused by irregular metallic fragments, the soft tissues, ribs and hepatic parenchyma may be extensively fragmented and devitalized. In addition fragments of clothing, splinters of bone and pieces of metal contribute to the contamination and favor the persistence of infection. Even a smooth and cleanly penetrating high-velocity bullet has sufficient kinetic energy to cause necrosis of tissues along its path through the liver and other organs.

The commonest location of the fistulous tract is between the posterior-superior surface of the right hepatic lobe and the diaphragmatic surface of the right lower lobe, rarely the middle.

Whatever may be the pathogenetic mechanism, a diagnosis is usually easily established by the expectoration of bitter-tasting, yellow sputum which may vary in amount from several milliliters to more than one liter of liquid daily, this occurring in a patient who has reason for infection to localize in the biliary tract or subdiaphragmatic spaces. The sputum is typically alkaline in reaction, and yields a positive test for bile. Ordinary roentgenograms may show a basilar pulmonary infiltrate, pleural effusion, an elevated or fixed hemidiaphragm, an enlarged liver or sometimes air-fluid levels within the hepatic outline. None of these constitute pathognomonic signs of fistula. Attempts to outline the fistulous communication by the injection of radiopaque media instilled into the bronchial tree are doomed usually to failure, because the tract is tortuous, narrow, and lined with granulation tissue or exudate; also the pressure gradient is from the bile ducts to the bronchi. However, iodized oil bronchography may succeed in certain cases, and is indicated in long-standing cases to determine the presence or absence of bronchiectasis or pulmonary abscess, the existence of which may influence the therapeutic program. Generally, the lungs and bronchi appear to tolerate even lengthy exposure to bile surprisingly well.

Treatment

The therapy is ideally preventive. A sound knowledge of the surgical anatomy involved in biliary tract operations, correction of obstructive lesions in the extrahepatic bile ducts, early diagnosis and

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proper selection of antibiotics in the management of acute biliary infections will reduce the incidence of this dreaded complication.

In the management of wounds traversing the thoracic cavity, diaphragm and liver, adequate exposure for hemostasis, debridement of devitalized tissues and removal of foreign bodies are of prime importance. This usually means a combined thoraco-abdominal incision. After the necessary surgery has been accomplished, adequate drainage of both pleural cavity and subdiaphragmatic space must be obtained. After closure of the diaphragm with nonabsorbable sutures, the pleural space is drained by intercostal catheters, and the subdiaphragmatic space separately through the abdominal wall.

The possibility of spontaneous cure in a biliobronchial fistula without surgical intervention is small, and then only after a prolonged period of drainage with possible episodes of serious hemorrhage, metabolic derangements and remote infectious complications. Those cases of biliobronchial fistula which result from extrahepatic bile duct obstruction, as by stone or stricture, must be approached through a laparotomy to establish a normal flow of bile and reduce the biliary hypertension. Healing of the fistula will usually follow quite rapidly.

In very chronic cases, especially those of traumatic origin, a thoracic incision or thoracolaparotomy may be required with lysis of adhesions and decortication of the adherent lung, closure of the fistula, debridement of the liver, and removal of foreign bodies, followed by a meticulous repair of the diaphragm and *separate* drainage of the pleural and subdiaphragmatic spaces.

Case Report

R. G., Nos. 40-80-45, a white male barber of 64 years, was admitted to the New Haven Hospital with complaints of malaise, shortness of breath and coughing up of bile-stained material. About eight years before the present admission, the patient began to have episodes of postprandial epigastric and right upper quadrant pain, belching and flatulence with occasional nausea and vomiting. After two or three attacks in the summer preceding his admission, his urine became unnaturally dark and stools light in color. Therefore, his family physician obtained an X-ray study of the gallbladder which revealed multiple large and small stones. On December 17, 1953, five months before admission to this service, he underwent cholecystectomy and appendectomy in another hospital but the common duct was not explored. The immediate convalescence was a stormy one with high fever and mental confusion until drainage of a subdiaphragmatic abscess was accomplished after resection of the right 12th rib posteriorly. Two months later, when external drainage appeared to have ceased, the wound reopened one day and drained voluminous yellow-brown malodorous fluid. This drainage persisted for three weeks. One month before the present admission the patient developed dyspnea and an increasing cough productive of copious, yellow sputum with a bitter taste. The patient began again to have febrile episodes and drenching sweats but no abdominal or chest pain. He lost 30 pounds in weight. His ankles began to swell markedly; he was comfortable only in the sitting or standing position; reclining caused a marked increase in cough. His urine was noted to be intermittently dark or coppery red.

Physical examination on May 14, 1954 revealed a well-developed but wasted, elderly, dyspnoeic white male confined to bed, coughing markedly and raising large amounts of bile-stained sputum. T. 103.2; P. 140, R. 32 and B.P. 154/70. The skin was moist and sallow but not frankly icteric. There was a right internal strabismus. A healed incision was noted over the right posterior twelfth rib. Abundant coarse moist rales were heard over the right chest below the level of the fifth rib with dullness to percussion at both lung bases. In the right upper abdomen was a healed oblique incision with a large incisional hernia in its central portion. No enlarged viscera, masses or tender areas could be palpated. The prostate gland was enlarged, smooth and non-tender. There was moderate pretibial pitting edema and distension of the superficial leg veins with localized varices of the right pretibial region.

Admission laboratory studies included an R.B.C. of 4.8 million; Hgb. 14; Hct. 45; W.B.C. 15,000, 89% polys, 6% lymphs and 5% monos. A urinalysis was negative. The sputum yielded a positive test for bile and a pH of 7.5. Serum bilirubin was 1.94 direct and total 3.20. BSP retention 34.1%; cephalin flocculation 2+ in 24 hours; alkaline phosphatase 58.2.

The patient was placed on aureomycin, 1.5 Gm. per day and his temperature fell rapidly to normal and remained so. He was able to take a diet containing 200 Gm. protein, 500 Gm. carbohydrate and 20 Gm. fat moderately well. Standard X-rays of the chest demonstrated upper lobe fibrocalcific changes and bilateral lower lobe infiltrates with a minimal right pleural effusion and an immobile right diaphragm. An upper GI series revealed a soft tissue density in the right upper quadrant, compatible with an inflammatory mass, and multiple diverticuli of the third part of the duodenum. An intravenous cholangiogram was attempted later and resulted in no visualization of the biliary tree. A bronchogram, after instillation of 5 cc. radiopaque material into the right lower lobe, showed no fistula or extravasation from the lung.

On the antibiotic program, postural drainage three times daily and diet as mentioned above, the patient improved greatly. The clinical impression was that of retained common duct stone or bile duct injury with subhepatic or subdiaphragmatic bile abscess eroding into the right lung and producing a biliobronchial fistula. Nineteen days after admission, on 6/3/54, the abdomen was explored through the original wound and a single large calculus was removed from the distal common duct which measured two cm. in diameter. A No. 9 Bakes dilator then passed readily into the duodenum. The common duct was drained with a T-tube and the wound closed incidentally effecting a repair of the incisional hernia. There was a profuse drainage of bile postoperatively through the T-tube. The patient's cough and bile-stained sputum ceased rapidly over-night, and his further convalescence was smooth. A postoperative cholangiogram showed good filling of the biliary tree, no retained stones or stricture and a free passage of the contrast medium into the duodenum. The patient was discharged on the fifteenth postoperative day with the T-tube still in position; he tolerated clamping of the tube for prolonged periods. It was allowed to remain for six months before its final removal and healing was complete thereafter.

Discussion

This case illustrates clearly one possible sequence of events following inadequate surgery for cholelithiasis which had involved the common duct in obstruction and ascending cholangitis. The subdiaphragmatic abscess in this case may well have resulted from an intraperitoneal leakage and accumulation of infected bile. The posterior 12th rib approach was inadequate for drainage or was undertaken too late to avert perforation of the diaphragm and the establishment of a bronchial fistula.

Correction of the biliary obstruction at *laparotomy* by removal of a large choledochal stone resulted in a dramatic cessation of the bilious bronchial drainage and healing of the fistula.

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Proper Use Of Words

The chief source of inaccuracy in the transfer of information is, I think, the use of technical jargon. On another occasion, in your country [United States], I devoted a little time to the way in which scientists nowadays fence off their subject with technical terms, so that those who have not first learned the language of the specialty cannot understand what the author is trying to say. Those of us who teach and work in the field of cardiovascular diseases are not entirely blameless in this matter. This is, if you like, a manifestation of the growth of nationalism in science, just as the move to teach in Erse, in Welsh, in Afrikaans, and other tongues is one example of the growth of nationalism within the general cultural life of the British Commonwealth. This is important. Nevertheless, I will say no more of it. I want to deal rather with . . . the transfer of information from the mind of the patient to that of the doctor. . . .

In taking a history of the patient's illness, I teach my students that they are eliciting an account of the patient's experience. They must use the patient's own words, provided always that both the patient and the doctor are sure that the information conveyed in these words is so far as possible accurate and unequivocal. They must never use terms, like "chesty," which means nothing at all. Nor must they use technical terms, such as anginal pain, or asthma, bronchitis, haemoptysis, or haematemesis, because these are not terms descriptive of experience but are terms that attempt to interpret that experience. Used by the patient, they are often used wrongly, as also indeed they are sometimes by the doctor, who, in using them, prematurely comes to a conclusion. To my mind a good history is one that is expressed entirely in words that are as simple and well known to us as the words used to describe events in the old and new testaments of the Bible. And I suspect we would all agree that a good history is perhaps the most important part of the evidence that takes us to an understanding of our patient's disability.—Pickering, G.: Medicine's Challenge to the Educator, *Brit Med J*, 2:1117-1121 (Nov 8) 1958.

Thorotrast-induced Hemangioendothelioma Of Liver

(A Case With Thirty-year Latent Period)

Daniel Kahn, M.D.

■ Thorotrast is a colloidal solution of 19-20% thorium dioxide, a radioactive substance. Since it was first introduced in medical practice by Bluhbaum, Frik and Kalkbrewer in 1928[1], it has been used as a contrast medium in a variety of radiological procedures. The reticuloendothelial system takes up the intravenously injected particles and the highest concentration is found in the liver and spleen;[2] so that one of its uses has been to produce a hepatogram and lienogram.[3] Radt[4] described this capability of rendering the liver and spleen radiopaque in 1930.

The disintegration of Thorotrast is associated with emission of alpha, beta and gamma radiation. Its half life is 1.39 x ten years; the breakdown products are active and reach a peak after fifteen years. Because of this radioactivity, the AMA Council on Pharmacy and Chemistry in 1932[5] warned against its possible tumor-producing potential. Its carcinogenic properties had been demonstrated experimentally in the laboratory in rats,[6] guinea pigs,[7] and rabbits,[8,9] before MacMahon[10] and his associates reported in 1947 the first case of malignant tumor that could be attributed to the injection of Thorotrast in man. Subsequently, many cases of neoplastic lesions have been reported following Thorotrast injection,[11-16] the large majority of these tumors occurring, as expected, primarily in the liver and biliary ducts. Baserga et al,[1] in 1960, reviewed 37 cases of cancer in man induced by Thorotrast and found 19 of these in the liver and extrahepatic ducts. Nine of these were endothelial cell sarcoma or hemangiosarcoma. The latent periods of development of hemangioendothelioma or endotheliosarcoma were long, ranging from 12 to 24 years (plus one exceptionally short interval of three years. The average was 14 years.) Another series[17] of 22 Thorotrast-induced liver hemangioendotheliomata showed a latent period of 20 years or more, with only one exception. Looney[18] suggested that hemangioendothelioma of the liver seems to be the predominant type of tumor seen emerging after Thorotrast exposure. He recognized that a mean latent period of 15 years is to be expected in this group.

The following case is reported as another instance of hemangioendothelioma of the liver, diagnosed antemortem, with an exceptionally long latent period of 30 years from time of injection to time of recognition.

Case Report

The patient, a 55-year-old white male arts instructor was hospitalized at the Meriden Hospital for the first time in 1933. At that time, an extensive workup for joint disease included the injection of 25 cc of Thorotrast intravenously over a three-minute period, in order to exclude a suspected liver abscess. The liver and spleen were outlined by the Thorotrast and appeared normal. Subsequent abdominal films in 1959 again revealed the hepatosplenogram. In 1959, during investigation for chest pain, liver function tests were normal except for cephalin flocculation of 4+ and alkaline phosphatase 24 King-Armstrong units.

The patient was hospitalized in July of 1963 with a mild anteroseptal myocardial infarction documented by electrocardiographic changes and significant but transient LDH transaminase rise. Alkaline phosphatases were 33 and 41 K-A units.

Eleven days prior to his final admission, he experienced colicky abdominal pain. A few petechiae were noted on the right shoulder, but abdominal examination was not remarkable. He then developed progressive abdominal enlargement, constipation, evening fever, weakness, anorexia, light-headedness, darkening of urine, light-colored stool, and was admitted on Sept 27, 1963.

Physical examination revealed blood pressure 130/70 mm Hg, pulse 90, temperature 99° F (oral). Positive findings included mild icterus of the skin and sclerae, moderately elevated diaphragm with abdominal enlargement due to ascites. The liver edge was full, soft, tender, palpable 6 cm inferior to the right costal margin. The spleen was not palpably enlarged. A trace of edema of the legs was noted. The initial impression on admission was acute infectious hepatitis.

X-ray Data: Initial abdominal films were consistent with ascites, and radiopacified liver and spleen were seen. Chest film revealed disc atelectasis at the right base and possible small right pleural effusion. Upper gastro-intestinal series on Oct 4, 1963, was normal. Chest and abdominal films on Oct 9, 1963, revealed enlarging liver and rapidly increasing right pleural effusion.

Laboratory Data: On admission white blood cell count 10,800 with differential shift to the left. Blood urea nitrogen 17 mg/100 ml, glucose 140 mg/100 ml, Hb 11.3 g/100 ml, prothrombin time 15 seconds, (control 13 seconds). SGO 40,

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SGP 16, LDH transaminase 600 units. Bilirubin 2 mg/100 ml; alkaline phosphatase 65 K-A units.

On Sept 30, 1963: Hb 7.4 g/100 ml, reticulocyte count 5.2%, hematocrit 25%. Coomb's test direct positive. On Oct 1, 1963: Blood urea nitrogen 40 mg/100 ml, total bilirubin 3.8 mg/100 ml, with indirect reacting bilirubin 1.35 mg/100 ml, Hb 8.9 g/100 ml, reticulocyte count 4.7%, platelet count 75,000, serum iron 62 gamma per cent. Tests of bleeding and clotting time, clot retraction time, prothrombin consumption were normal. There was partial fibrinolysis of the clot at 24 hours. Acid phosphatase 0.3 units. SGO 42, LDH 800 units. Paracentesis fluid revealed 3,400 white blood cells (50% polymorphonuclear, 11% stabs, 5% monocytes and 7% atypical mononuclear cells). Cell block and Papanicolaou smear showed two groups of unusual cells varying from the normal mesothelial cells. Sternal marrow aspiration biopsy was not remarkable. On Oct 5, 1963, alkaline phosphatase had risen to 87 K-A units. Coomb's test was weakly positive. LE prep was negative, urine for Bence-Jones protein negative.

On Oct 8, 1963, platelet count was 130,000; alkaline phosphatase 118 K-A units; SGO 66, LDH 1080 units; bilirubin 2 mg/100 ml.

Hospital Course: Patient was treated with mercurial diuretics, bed rest and high caloric, low sodium diet on admission. It was apparent on admission that the liver function tests were not characteristic of hepatitis and the possibility of a neoplasm with spread to liver and peritoneum was considered. On Sept 30, 1963, he developed marked pallor and weakness with hypotension and tachycardia. Laboratory data revealed a possible acute acquired hemolytic anemia and he was given two units of blood and started on large doses of prednisone. Paracentesis on Oct 1, 1963, produced 4.5 liters of grossly bloody fluid. While on prednisone 40 mg daily, the platelet count gradually rose and the hemoglobin stabilized. The liver was noted to be enlarging and tender. On Oct 9, 1963, he developed signs of increasing right pleural effusion. The increasing elevation of alkaline phosphatase suggested hepatic tumor. On Oct 10, 1963, he had sudden epigastric pain and tenderness, pallor, weakness, nausea, and the blood pressure fell to 70/40 mm Hg. The liver was felt to be further enlarged; this episode was interpreted as a possible subcapsular hepatic hemorrhage. He received blood transfusion, oxygen administration, demerol and metaraminol. On Oct 11, 1963, it was recognized that the entire clinical picture, including intra-abdominal hemorrhage, could be explained on the basis of hemangioendothelioma of the liver, etiologically related to the 1933 Thorotrast injection. On Oct 13, 1963, he again lapsed into shock with extreme pallor, abdominal pain radiating to the back, and further abdominal enlargement. Urine output fell and he became more icteric with asterixis and fetor hepaticus. Signs of hepatic failure increased and he expired on Oct 14, 1963.

Autopsy Findings

A huge hematoma involved the lower half of the anterior abdominal wall and extended around the umbilicus and into the anterior surface of the scrotum. Scleral icterus was present. The right pleural cavity was filled with dark bloody fluid. Approximately 3,000 cc of blood was found free in the peritoneal cavity. A large (12 cm diameter) hematoma was in direct connection with the liver parenchyma. The spleen was small, calcified, firm and shriveled (5 x 3 x 2 cm), surrounded by firm fibrous adhesions. A firm nodule was felt in the adhesions between the omentum and anterior liver surface. This was dark brown to red on sectioning. A similar mass was wrapped within the omentum. There were additional multiple hemorrhagic nodules and a conglomerate of several in the right hepatic lobe. In addition, many spongy nodules of brown color surrounded by yellow, showing many newly formed vessels, were distributed in irregular fashion over the hepatic parenchyma. The parenchyma not involved by tumor had a firm gray-to-yellow nodular appearance suggestive of cirrhosis. The liver measured greatest diameters of 23 x 17 x 9 cm. Lymph nodes of the thorax and abdomen were free of tumor.

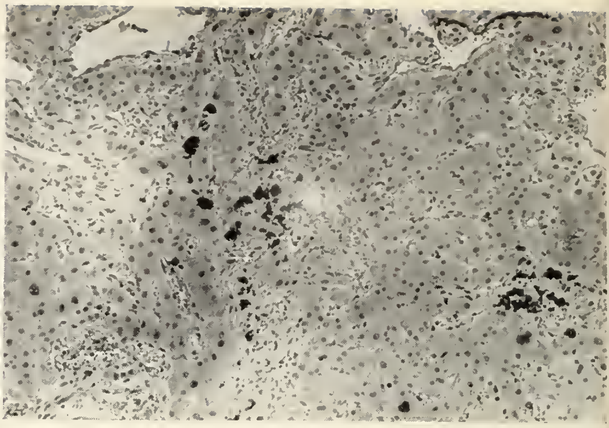

Figure I

Newly formed endothelium-lined space extending into lobules of liver. Note thorium-laden monocytes. (Hematoxylin and eosin, x 90).

The hepatic tumor, histologically, consisted of bunches of newly formed capillaries as well as systems of newly formed endothelial-lined spaces. Some of the newly formed systems showed a few individual or small groups of liver cells remaining (Figures 1,2,). There was central necrosis of the nodules. Foreign matter, partly iron, partly remnants of thorium dioxide (Figure 3) were seen both in liver cells as well as in the Kupfer cells. They were within mononuclear

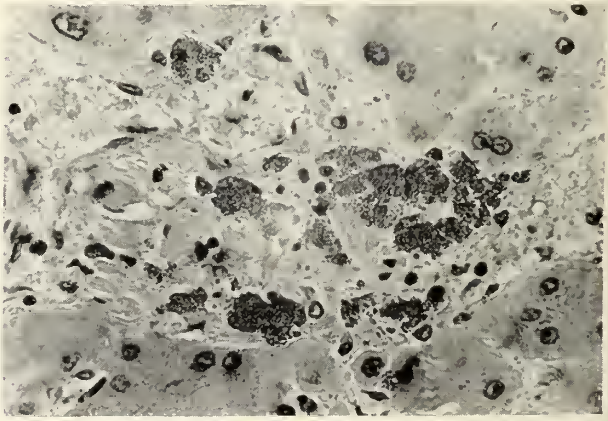

Figure II

Thorium-laden monocytes in liver. (Hematoxylin and eosin, x 220)

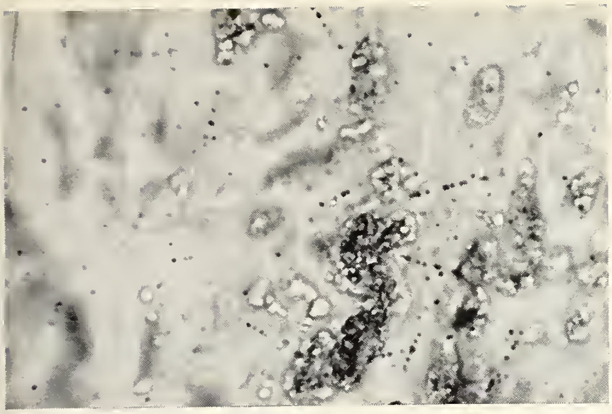

FIGURE III

Alpha particle tracks in region of thorium-laden monocytes in liver. (Autoradiograph, hematoxylin and eosin, x 900)

elements and free in the interstitium of the newly formed vascular tumor.

Anatomical Diagnoses:

1. Thorium storage in liver, spleen and lymph nodes
2. Cirrhosis of liver
3. Fibrosis and atrophy of spleen
4. Hemangioendotheliomatosis of liver
5. Adhesions of omentum to liver
6. Recurring massive intraperitoneal hemorrhage

Comment

The diagnosis of Thorotrast-induced cancer in this man rests on the demonstration of radiopaque deposits in the liver and spleen, confirmed by autoradiography, and the pathological demonstration of lesions widely reported in association with Thorotrast injection.

This case is of especial clinical interest in that the latent period, from injection of Thorotrast to time of recognition of the neoplastic lesion, was as long as 30 years. The stepwise increase in alkaline phosphatase over the last four years of his life was the only indication of a slowly progressing hepatic lesion; other liver function tests were normal until the terminal illness, characterized by intra-abdominal hemorrhage, hepatic enlargement and decompensation, and profound anemia with shock. Looney[18] described these hemangioendotheliomata of liver as being slowly progressive, terminating fatally due to replacement of the liver parenchyma, and manifested by enlarged liver, anemia and fever.

Hemorrhage from the liver has been described as a frequent cause of death both clinically[10] and in laboratory animals. Zeitlhofer and Speiser[19] found multiple hemangioendotheliomata in the liver, spleen and lungs of a rabbit injected with Thorotrast four years previously. Its death was caused by rupture of one of these lesions.

There seems no doubt that the many cases of neoplasms of the liver and biliary ducts reported after Thorotrast injection have established a causal relationship. That the 25 cc dose employed in the present case was a significant one radiobiologically, can be illustrated by its equivalent in radium. Budin and Gershon-Cohen[20] have pointed out that the alpha radiation emitted by 25 cc of Thorotrast is equivalent to that produced by 0.5-1 microgram of radium. Fatal poisoning of painters of luminous watch dials indicated that the amounts involved were approximately 0.5-2 micrograms of radium. They emphasized that the dangers of carcinogenesis outweighed the advantages of Thorotrast as a general diagnostic medium.

Thus, as Horta et al[17] warned in 1965, after reviewing twenty-two cases of liver hemangioendothelioma attributed to Thorotrast injection, no apparent justification exists for the use of Thorotrast in any patient with a life expectancy of more than two years.

Summary

A case of fatal hemangioendothelioma of the liver attributed to Thorotrast injection is reported, with an unusually long latent period of thirty years.

The similarity of the pathology to those of other clinical and laboratory-induced cases adds to the probability that liver hemangioendothelioma is the most common neoplastic lesion induced by Thorotrast.

Further emphasis is placed on the danger of Thorotrast as a diagnostic medium in medical practice.

Acknowledgement

Rolf Katzenstein, M. D., Pathologist, Meriden Hospital, prepared and interpreted the pathological specimens. The autoradiographs were prepared by Dr. Peter Hukill, Associate Professor of Pathology at the Yale University School of Medicine.

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Society's Section On Ophthalmology Announces Meeting

Andrew S. Wong, M.D., President of the CSMS Section on Ophthalmology, has announced that there will be a fall meeting of the Section on Wednesday, October 11, 1967, at New Haven.

The meeting will open with an afternoon program, to be held at the Eye Clinic of the Yale-New Haven Medical Center, starting at 1:30 P.M. Robert Hollenhorst, M.D., Professor of Neuro-ophthalmology at the University of Minnesota and the Mayo Clinic, will conduct a clinic in neuro-ophthalmology, assisted by Thomas Walsh, M.D., Assistant Clinical Professor of Neuro-ophthalmology at the Yale School of Medicine. At the conclusion of the clinic presentation, a brief business meeting of the Section will take place at 4:30 P.M.

In the evening, starting at 6:00 P.M. at the Park Plaza Hotel in New Haven, there will be a reception and dinner in honor of Dr. Hollenhorst, following which he will speak on "Retinal Arterial Occlusive Disease as a Manifestation of Systemic Vascular Disorder."

Any physician interested in attending the reception and dinner is asked to make reservations before October 3 with: Daniel M. Taylor, M.D., Secretary, CSMS Section on Ophthalmology, c/o Grove Hill Clinic, New Britain, Connecticut.

Uterine Perforation By The Intrauterine Contraceptive Device

Peter A. Goodhue, M.D. and Walter S. Ridgway, M.D.

Medical advances are often accompanied by overzealous enthusiasm which is subdued only by continued experience. The renewed excitement for the intrauterine contraceptive device has been calmed by bothersome side effects and expulsion. A rather serious complication, uterine perforation, has previously been reported with use of the Grafenberg ring.[1,2,3,4,16,17,19-20] The newer devices have been found not to be immune to an ectopic location. Tietze[23] reported the frequency of perforation after insertion of 25,427 of the newer devices. He found the perforation incidence to be 0.7 per 100 insertions for the Birnberg bow and 0.04 per 100 insertions for the spirals, loops, and steel rings combined. Review of the literature to date reveals the present number of reported cases of uterine perforation with the intrauterine contraceptive device to be as follows: Birnberg bow, 53;[12,15,18,21-23] Lippes loop, 9;[3,12,14,23] Marguiles spiral, 6;[4,5,10,23,24,25] and Ultrathene ring, 1.[6]

Gynecologists in the Stamford area are using the Lippes loop and the Marguiles spiral. Over the past year there were 2 recognized cases of uterine perforation, one with each of the two types of device used. These cases are reported and the literature reviewed with the purpose of making suggestions that might decrease further this unfortunate complication.

Case Reports

Case 1. C.D., a 20-year old gravida 2, para 2 had a Marguiles spiral placed at 8 weeks postpartum. Her Gynecologist noted the uterus to be in a retroverted position, but the spiral was introduced with ease. 4 days following insertion the cervical bead was not felt by the patient or visualized by her physician.

Frontal pelvic roentgenography (Fig. 1) showed the device to be more to the right than expected. A lateral view suggested that the device was in a normal location. A third radiograph (Fig. 2) taken with a metal sound in the uterine cavity revealed a marked displacement of the spiral to the right pelvis.

The patient was hospitalized on June 23, 1965. Physical examination and laboratory studies were normal. Pelvic examination under anesthesia revealed the uterus to be retroverted, mobile, and soft. The uterine cavity was explored, and the device was not located. Pelvic laparotomy revealed the spiral to be free in the pelvic peritoneal cavity. There was a small punctate defect in the anterior uterus just above the vesico-uterine fold. The device was removed, and no further surgery performed. She was treated with antibiotics postoperatively and recovered uneventfully.

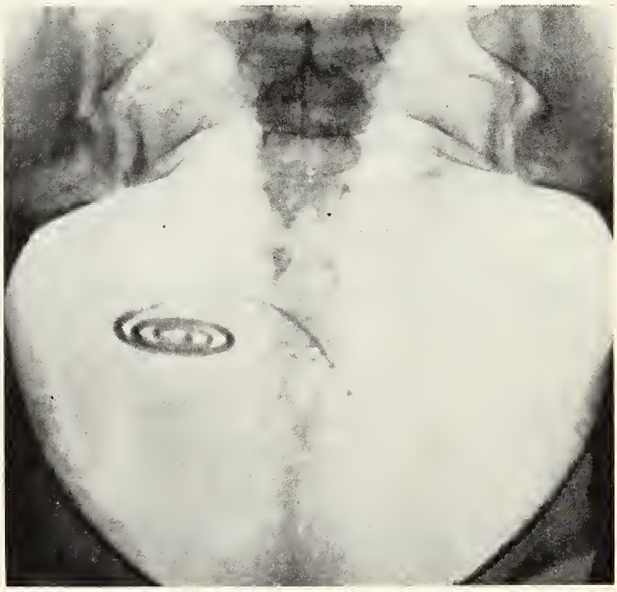

Figure I

Frontal pelvic roentgenograph showing a Marguiles spiral deviated to right pelvis.

Case 2. L.R., a 21-year old gravida 4, para 4 had a Lippes loop placed at 6 weeks postpartum. The Gynecologist noted the uterus to be markedly retroflexed, but the insertion was performed with ease. On July 12, 1966, 3 months following insertion she was admitted to the hospital with fever and lower abdominal pain. Her symptoms began following the third menses after insertion. She stated that 2 weeks prior to admission she could feel the vaginal strings.

Physical examination revealed the oral temperature to be 101 F. The abdomen was tender with rebound in the lower quadrants. Pelvic examination showed a foul cervical discharge, culture of which later grew out Staphlococcus albus and Diptheroids. The uterus was of normal size, tender, and fixed in a retroflexed position. There was bilateral adnexal tenderness.

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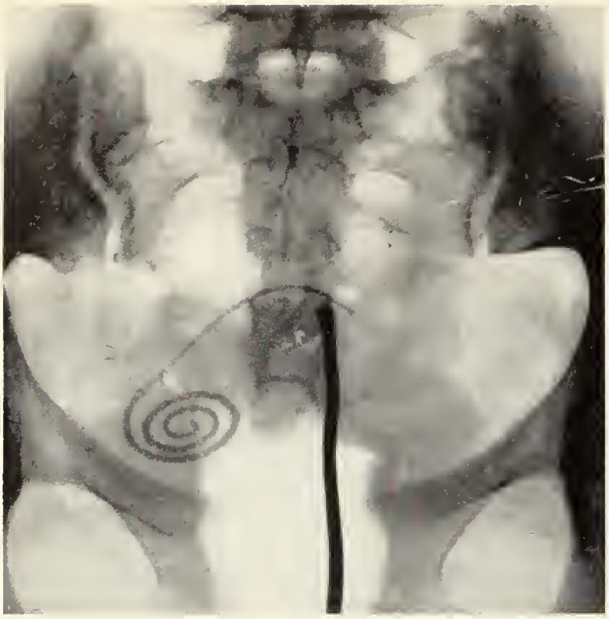

Figure II

Frontal pelvic roentgenograph with a metallic sound in the uterine cavity. Marguiles spiral markedly displaced to the right pelvis.

Frontal pelvic roentgenography showed the loop to be more to the left than expected. A lateral radiograph (Fig. 3) showed the loop to be completely turned around so that the string end faced the sacrum.

She was taken to the operating room and exploration of the uterine cavity under anesthesia failed to identify the device. Pelvic laparotomy revealed the device to be in the left cul de sac beneath a fixed retroflexed uterus. There was a gray exudate in the cul de sac, filmy adhesions over the pelvic organs, and grossly inflamed fallopian tubes. There was a puckered area in the posterior uterine which was thought to represent the point of performation. The device was removed, and no further surgery performed. Culture of the cul de sac fluid failed to reveal any organisms. Postoperatively she was treated with antibiotics, and after the second postoperative day she remained afebrile. Her recovery was uneventful.

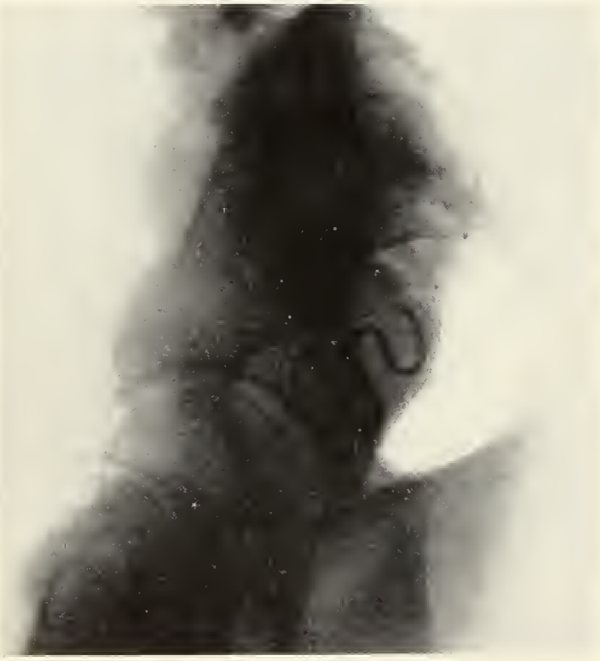

Figure III

Lateral pelvic roentgenograph showing a Lippes loop with the string end facing the sacrum.

Comments

Uterine perforation by an intrauterine device is uncommon. Earlier authors proposed the possibility of devices migrating through the uterus after being properly introduced.[1,2,7,9,17] Recent investigators suspect perforation at the time of insertion as the etiology of extrauterine locations.[10,12,24] Our second case is of particular interest in that at first glance it appears that the loop migrated from an intrauterine position to an intraperitoneal location nearly 3 months following insertion. We suspect that a partial perforation occurred at the time of insertion allowing the strings to still be present in the vagina, and the device was completely extruded into the peritoneal cavity at a later date.

Unfortunately most cases reported are merely mentioned with the presentation of a large series of insertions. Those cases reported in detail were most helpful in evaluating this problem.[3,4,5,6,10,14,15,18,19,21,22,24,25] The large majority of perforations occurred when the insertion was performed at 6 to 8 weeks postpartum, and many of the operators stated that the insertion was done with ease. This was the situation in both of our cases. In Tietze's large series of insertions the perforation rate was 3.4 per 100 insertions at 5 weeks postpartum, and 0.2 per 100 insertions at 3 months postpartum. It also became evident upon reviewing the detailed reports that many uteri were ante or retrodisplaced at the time of insertion. Both of our cases had retrodisplaced uteri. It seems probable that uterine perforation would occur less often if the insertion was delayed until the second menses following delivery, especially in those uteri that are ante or retrodisplaced. A more completely involuted uterus would be present at this time.

Most cases of an intraperitoneal device can be diagnosed by routine anterior and lateral roentgenography. It has been demonstrated that the beolocator and hysterogram can solve the more difficult problems.[10,11,12,15,18] We found that a radiograph with a metal sound placed in the uterine cavity to be a simple and helpful diagnostic procedure.

The seriousness of this complication is supported by the fact that all those cases reported in detail were subjected to pelvic laparotomy. It has recently been suggested that an intraperitoneal device need not be removed if the patient is asymptomatic.[25] All the cases we reviewed were subjected to surgery soon after the diagnosis of an intraperitoneal location was made. Many of the asymptomatic patients operated upon were found to have the device adherent to omentum. We would fear that a foreign body in a "fixed" position might at some time cause intestinal obstruction. There are 4 reported cases of intestinal obstruction; 2 of these patients were asymptomatic for as long as 6 months following insertion.[6,19,21,22] Bowel resection was performed on 3 of the patients because of strangulation gangrene. The devices used were of the closed type, ring or bow. In 3 cases the device was in a fixed position in that it had partially perforated the uterus, but in one case the device was found to be lying free in the peritoneal cavity with incarcerated bowel in it. Intraperitoneal devices of the open type, the loop or spiral, have not been reported in association with bowel obstruction. At present we favor the removal of all types of intrauterine devices that have entered the peritoneal cavity.

Summary

1. Two cases of uterine perforation with intrauterine contraceptive devices are reported, and other case reports are reviewed.

2. It is our opinion that all ectopic devices result from a partial or complete perforation at the time of insertion.

3. The possibility of perforation may be decreased if insertion is delayed until the second menses following delivery, especially in those uteri that are markedly displaced.

4. Comments are made concerning the diagnosis of an intraperitoneal contraceptive device.

5. At present we recommend removal of all intraperitoneal devices whether or not the patient is symptomatic.

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Transportation In Health Services

Jerome S. Beloff, M.D.

Introduction

In a rapidly changing society such as ours, with its increasing pace toward urbanization and multicity complexes, three of our most important problems are communication, coordination, and transportation. The successful provision of health services is intimately involved with communication between the consumer and provider of services and with coordination of needed services among our highly developed but fragmented specialty resources. A very sophisticated transportation network is required to bring the patients and services together. Our attention at this time is focused on the many aspects of transportation for health care.

The Needs

In examining health service transportation needs it might be helpful to consider the past, present and potential future patterns of health care. *Medical care in the past* concentrated on the acute episodic illness with emphasis on a correct diagnosis and appropriate treatment. As recently as 40 to 60 years ago there was very little scientific medicine as practiced today, and there was rare use of laboratory tests, X-ray, drugs, or specialist services. In that era of medical care transportation needs were minimal for the patient and the physician.

In the *present pattern of care* dating back approximately two decades, there have been social and scientific advances which have changed the entire nature of medicine. More accurate methods of diagnosis, plus the use of antibiotics and chemotherapy, have made the management of acute disease processes relatively easy. Infectious diseases are no longer the serious killers that they were just a relatively few years ago. There has devloped, therefore, increasing involvement with patients having chronic illnesses requiring medical management over long periods and necessitating multiple treatment visits. Scientific advances have led to the reliance on laboratory examinations, such as X-rays, electrocardiography, blood chemistry studies, and other highly technical services. The explosion of knowledge has led to the development of specialists fragmenting the total management of each patient into many specialty areas. In an effort to avoid depersonalizing medical care the philosophy of comprehensive health care is being developed. This involves the consideration of the medical, social, economic, emotional and environmental aspects of the health problems of the patient, in order to manage adequately his total health needs.[1]

A natural consequence of the increasing preoccupation with preventive medicine and chronic disease, and the reduction in the national death rate, is the development of an increasing number of elderly people in our society with chronic disease management problems. For proper comprehensive health care these patients require frequent contact with the specialized medical resources of the health establishment. This may involve social work counseling, physical medicine therapy, X-ray therapy, day hospital visits, and when most appropriate the home care services of several different specialists who must travel from the medical centers to visit the patients in their homes.

To reap the benefits of this modern scientific health care system, the economically secure family travels many miles each year in their private automobile. The social groups in our society, however, with the greatest health needs are the medically indigent and the elderly. Health transportation problems for these people, often crippled or infirm, are often complex and frequently the patients cannot provide their own transportation. The presently organized means for providing transportation to these patients is, more frequently than not, inadequate or nonexistant.

The recently enacted national legislation, Medicare and Medicaid, with its economic support for health services for the elderly (Title 18), and the disabled and indigent (Title 19), will most certainly increase the number of ambulatory patients and their transportation needs.[2] The Public Health Service estimates that by 1970, there will be 400 million patient visits per year to hospital ambulatory services.[3] This is double the number for 1960!

If the present efforts to improve our health care system continue, we can speculate on what the *future pattern of care* might be like. As the health

From a keynote address at the Connecticut Health League Statewide Conference on Transportation for Health Care, held January 18, 1967 at Connecticut General Life Insurance Company auditorium in Bloomfield, Connecticut.

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care programs become comprehensive and involve a larger portion of the population, the transportation needs of the patients and providers of services will become more complex. Let us consider a few of the newer concepts for future care.

The regional medical care programs for heart disease, cancer, and stroke, certainly make it evident that we will have considerably more centralization of specialized health resources in large hospital complexes.[4] These complexes will contain the very expensive instruments of modern medical therapy. Smaller hospital centers in an organized network of hospitals will handle problems within their capability and will refer the more involved management problems to the central complex. Planning for regionalized health services in Connecticut is already underway through a Federal grant to the two medical schools in the State—Yale, and the new University of Connecticut Medical School. This should lead to movements in both directions, i.e. patients to multiple medical centers, and specialists from the larger centers moving out to give consultation in the smaller units.

The idea of *neighborhood health centers,* particularly in the densely populated urban centers, is already being implemented on a demonstration basis in many areas of the country.[5] These centers will be located in the middle of highly populated areas of poverty families, and will contain health teams of physicians, public health nurses, health aides and social workers. This will put the health resource for continuing care and emergency care within easier reach of the patients. Because of the shortage of highly trained physicians and nurses for these expanding services, a new group of paramedical health aides is being developed to assist the professional core in giving the kind of comprehensive health attention which we know is needed.

Extended care facilities such as convalescent homes and nursing homes, with a close relationship to the hospitals, are being greatly expanded.[6] This will put an increased strain on transportation resources not only for the movement of patients and staff in both directions, but for transporting laboratory specimens to the central labs.

The development of *organized home care services*[7] will deliver public health nursing services, physical medicine treatments, rehabilitation programs, social services as well as specialist medical services to the patient at home, and thus will challenge our ingenuity for organization, trasportation, and for communication.

The *economic barrier to health services* for the poor is in the process of being removed by present legislation. It would appear that in the future prepaid health insurance for all will be the mechanism for paying for the needed health services. In defining schedules of payment transportation costs must be included as regularly as medical costs, drug costs, and appliance costs. In the coordinated health care system of the future there will have to be a well coordinated transportation network of ambulances, busses, limousines, helicopters, airplanes, and all means necessary to bring the patient and the health resource together. The city planning architects of the future are already giving transportation a very high priority, and are situating the hospital and health center near the core service area, such as the main shopping plaza.

The Concepts For An Effective Health System

The evolving improvements for our health system must be based on a set of initial assumptions which I should like to review briefly.

1. The ultimate, if not immediately available, goal is to provide good health services for our entire population, regardless of ability to pay. General agreement on this concept seems evident from the Social Security Amendments (Titles 18 and 19), the anti-poverty program, and the new PL89-749—the comprehensive health planning amendment of 1966. A recent statement by Dr. Charles Hudson, president of the American Medical Association, indicated that a "top priority AMA obligation" is to provide more and better health services for the needy.

2. A system of comprehensive health insurance coverage for all is needed to implement the first assumption. This seems to be evolving as a combination of public and private health insurance programs. The urgent need for this was stressed recently by Dr. George James, Dean of Mt. Sinai Medical School and former Commissioner of Health for the City of New York, who stated that he felt the number one cause of death in this country is not heart disease, cancer, or stroke, as is commonly thought, but in reality is poverty.[8] Poverty at present makes it so difficult for large numbers of ill persons to receive appropriate attention early, that their illnesses are neglected, and when they are forced to seek medical care the situation is often irreversible.

3. A new system is needed for the delivery of health services tailored to our present health needs. This means emphasis on preventive medical care, the management of chronic illness, and rehabilitation services for restoration of maximum function. To implement this provision we will need teams of health specialists with regional distribution in neighborhood, community, state, and national centers where specialized scientific equipment is available.

4. The present health manpower shortages require a more effective use of paramedical personnel,

particularly for preventive and routine health care, thereby freeing the limited number of professional physicians and nurses for more attention to disease diagnosis and management.

5. The modern hospital seems destined to become the community health center for complicated problems of diagnosis and special treatment, and the inpatient center for the acute patient, the continuing care patient, and the chronic disease patient malfunctioning for organic or psychiatric reasons. It seems evident from the very high cost of modern scientific care that the specialized and expensive equipment and personnel must be concentrated into a large central complex where they can be shared by patients in different stages of disease.

6. It is becoming more and more evident that we have a basic need for a health services transportation system for moving patients and services efficiently to and from the health facilities, and for bringing health resources to the homebound or institutionalized patient. The providers and financers of health services must accept the cost of transportation as an integral part of the cost of the medical service.

Transitional Period Suggestions To Improve Present Health Transportation Services

While awaiting the "brave new world" of the future there are many things that we can do now to improve the present health transportation facilities. I should like to consider a few of these in detail.

1. We can amass increasing support for the present existing transportation system. This includes the availability of trains, busses, ambulances, and volunteer groups such as the Red Cross. It is most essential that a basic minimum of train and bus transportation be maintained for that group in the population which does not have its own private transportation.

We are in desperate need of legislation to regulate the new disorganized complex of public, private, and volunteer ambulance services existing in this state and nation as a whole. At the present time we have no set of minimum standards for ambulance operation, no licensing procedures, and no mandatory training programs to assure adequate ambulance attendants. We can also work toward a coordinated ambulance coverage of our entire state with ambulance-to-hospital radio communication and central dispatching offices. In those towns where the Red Cross transportation is the main source of help for the medically indigent, it is urgent that it get more United Fund support. In the city of New Haven at the present time the Red Cross is operating on a schedule of two half-days per week.

2. We could certainly look to improving the access roads to the large medical centers used by many people each day. Around these well used health centers inadequate parking seems to be a perennial problem. Many patients are late for, or miss, their appointment because they ride around the block four or five times before finding an available parking space. There is a national need for better direction signs on highways to direct people with emergency problems to the nearest hospital areas. Many hospitals throughout the country with active emergency services fail to indicate clearly by prominent signs the location of their emergency service entrance.

3. In obvious medical emergencies we should be able to make more efficient use of the Police Department for transportation when other facilities are not available. Station wagons instead of coupes would be more appropriate in this regard. On January 4, 1967, Governor Dempsey suggested the development of a new Department of Transportation for the State of Connecticut. This would be the appropriate agency to implement the suggestions just made, if the new agency takes a look at total transportation needs, and not the usual focus on rail and air travel exclusively.

4. The Connecticut State Welfare Department reimbursement mechanism for welfare patients requiring transportation certainly needs revision. The Welfare Department in general is helpful, understanding and cooperative. However, their established administrative machinery for paying these transportation costs is often inadequate. This refers particularly to the welfare patient whose illness requires a series of treatment visits to a clinic, such as a person with cancer requiring a series of radiation therapy visits. The present regulation requires that the patient pay for his multiple taxi, bus or train trips from his meager basic allowance, then file a form for reimbursement at the end of the series of visits. If everything goes well, three months after that date he may receive a repayment check. For the average welfare family, struggling to balance its food and housing budget, there is no surplus cash for advancing monies for this kind of transportation, and because of this, needed services are often neglected. Yet, a simple transportation voucher signed by the clinic social worker or physician could authorize the transportation payments and allow the transportation company to be reimbursed directly from the Welfare Department. The Yale-New Haven Hospital, operating as most teaching hospitals do, at an annual financial loss, pays approximately four to five thousand dollars per year for taxi slips to welfare patients who need emergency transportation to their home following a visit to the emergency service or to one of the clinics. This is due to a welfare requirement which provides no reimbursement for this type of transportation unless prior authoriza-

tion is obtained, and this is often not possible. Despite these inadequacies, the Welfare Department does have a verbal approval mechanism for welfare requiring emergency ambulance transportation from one area to another.

5. With aroused community support, the process of establishing neighborhood health centers in high density population areas, such as housing projects, can be greatly speeded up. This one step would reduce the need for long distance transportation of large numbers of people. When the health centers are established and functioning they should certainly develop transportation pools with available station wagons and trained personnel for transporting their health center patients to special treatment centers for scheduled appointments. Smaller towns may have to develop a volunteer transportation corps for health transportation just as they have developed a volunteer Fire Department.

6. In areas of low density population—such as sections of Colorado, Utah, and Alaska—this transportation problem is being solved by travelling clinics which spend one day in each of many scheduled centers.[9] Some of these areas already have flying physicians who conduct office hours in widely scattered centers through their own private air travel. The Viet Nam experience has taught the importance of the helicopter in bringing the seriously wounded patient to a well equipped emergency center as a way of saving many lives. Dr. Robert Kennedy has estimated that there are approximately 100,000 deaths in this country annually from accidents. It is also estimated that 20,000 of these victims would not have died had prompt and competent emergency care been available to them.[10] Helicopter ambulance teams operating out of state police barracks may be a way of life in the not too distant future.

7. Another innovative idea which is receiving experimental trial in New York City at the present time is the development of "store-front" health screening stations throughout large metropolitan areas.[11] These screening stations are manned by public health nurses or physicians and help the patients decide where they can receive the most appropriate medical services. Many of these patients merely need counselling and advice, whereas others need referral to a large hospital clinic for diagnostic workup. These screening clinics function to reduce the number of patient transportation units per day, and also increase the distribution of medical care to a considerably larger segment of people than would be provided without them.

Summary

Social, scientific and political changes have helped to produce a complex, fragmented system of medical care. The development of more involvement with chronic illness and the increasing emphasis on preventive medicine require health maintenance visits at periodic intervals over time. Many changes needed to rationalize and coordinate this complex, poorly functioning system, have been discussed. New patterns in the distribution of medical care services have been pointed out; these include neighborhood health centers, regional health programs, extended care facilities, and organized home care services. It is clear that efficient and sophisticated transportation facilities are needed in increasing amounts to bring together the patients and the health services of our present society.

To develop an adequate health care system for all Americans, this difficult transportation challenge must be met promptly. This state conference—the first ever held to consider the subject of transportatoin for health care—is a giant step forward in identifying the needs and making them known. The innovative energies of the Connecticut Health League, which made this conference a reality, must next be directed toward the implementation of solutions to the problems posed by the conference participants.

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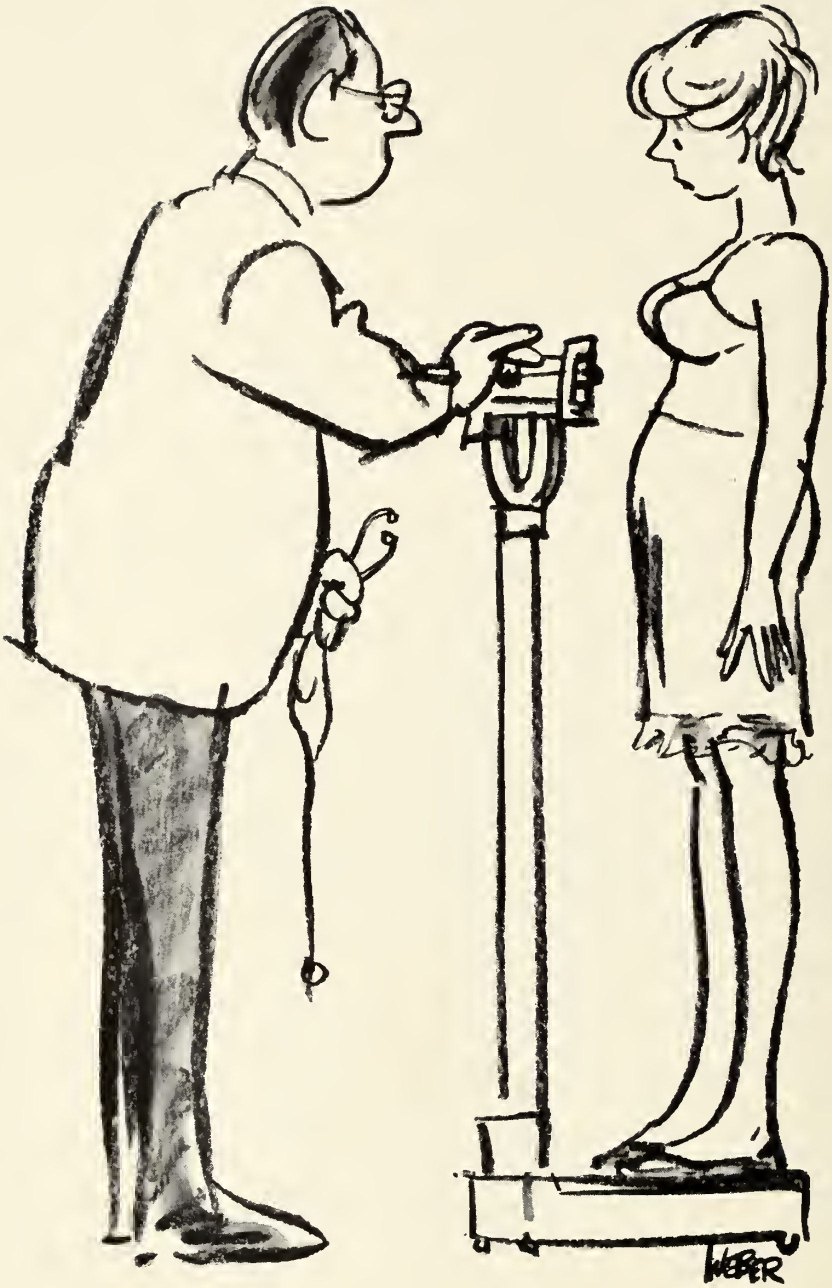

"You're up ten pounds since your last physical. We're going to have to do something about that."

Get them while they're easily reversible.

Obesity doesn't happen suddenly. This insidious process has its beginning—and the chances of reversing it are better—during the *first 10 to 15 pounds of weight gain.* When a new dietary pattern must be established, consider the adjunctive use of BAMADEX SEQUELS. Combining the proven *anorexigenic* action of d-amphetamine with the *tranquilizing* effect of meprobamate, BAMADEX SEQUELS controls appetite throughout the day, usually with a single capsule daily.

Contraindications: Dextro-amphetamine sulfate: In hyperexcitability and in agitated prepsychotic states. Previous allergic or idiosyncratic reactions to meprobamate.

Precautions: Use with caution in patients hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease, or are severely hypertensive.

Dextro-amphetamine sulfate: Excessive use by unstable individuals may result in psychological dependence.

Meprobamate: Careful supervision of dose and amounts prescribed is advised, especially for patients with known propensity for taking excessive quantities of drugs. Excessive and prolonged use in susceptible persons, e.g. alcoholics, former addicts, and other severe psychoneurotics, has been reported to result in dependence on the drug. Where excessive dosage has continued for weeks or months, reduce dosage gradually. Sudden withdrawal may precipitate recurrence of preexisting symptoms such as anxiety, anorexia, or insomnia; or withdrawal reactions such as vomiting, ataxia, tremors, muscle twitching and, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, reduce dosage and avoid operation of motor vehicles, machinery or other activity requiring alertness. Effects of excessive alcohol consumption may be increased by meprobamate. Appropriate caution is recommended with patients prone to excessive drinking. In patients prone to both petit and grand mal epilepsy meprobamate may precipitate grand mal attacks. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness. Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Sustained Release Capsules

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THE PRESIDENT'S PAGE

Perhaps there's a basic schizophrenia in the practice of healing. A hundred years ago only a few definitive surgical procedures were performed and, lacking adequate biochemical research, most medication was dispensed empirically. Through years—and even generations—of knowing his patients, their families and circumstances, the physician was able to compensate for his deficiency in scientific armamentarium by artfully administering to the psychologic and spiritual needs of his people sage advice about a business change, a wayward child or an aged grandparent who rocked incessantly by the hearth.

At the June convention of the AMA, a Dr. Gustav Nossal reported the Australian studies of the attack of antigens on the lymphocytes to produce antibodies, and the variation in effect depending upon the size of the antigen or the type of the lymphocyte. This tremendous work on things so small may overcome some major problems of organ transplantation. Science has scaled the Matterhorn, has ascended to another in a series of peaks, yet is just starting to climb. But how cold is it up there? Though I can climb—or move—mountains and have not love, I am nothing. The family practitioner has greater opportunity to dispense the warmth and understanding which made so effective those colorful pills of last century. Yet this is not—and must not be—beyond the duty of the specialist. Are we treating patients?—or just disease! The practice of medicine entails both the science *and* the art.

Who shall have a new aorta, a new kidney or lung, indeed who shall have a new heart or a rejuvenated blood supply to the brain? When, after substitution of multiple "spare parts", is a person permitted to die—or is this now a different individual? This approach to immortality is unlikely to quell the population explosion. But should these services be denied to anyone? Perhaps a mandatory control of conception might function under a system of licensure and penalties—more economical to both health and finances than extending abortion. These thoughts and many more come to our minds. The physicians and the clergy jointly bear a large responsibility for guiding the progress of society. Yet each specific case demands a decision. For this each physician needs a set of principles or criteria.

Yet the quality of a piece of sculpture or a painting cannot be determined by measurements alone. Neither must the physician be too rigidly shackled by rules, ethics, or law. He must be free to practice the art of medicine in making the best decision for his "whole patient": in balancing possible scant benefits and a grim life against acceptance of "the inevitable" with its byproducts; in permitting the right to die with dignity even though it might be a few hours or days earlier; in struggling to prolong a life that would be of value to the patient or someone else; in actively supporting anyone's right to try to live. He must most of all be at peace with his own conscience. "Unto thine own self be true," and you will be true to your fellow man.

Speaking of children in *The Prophet*—and our patients are comparable to our children, "though they are with you, yet they belong not to you"—Kahlil Gibran said ". . . life goes not backward nor tarries with yesterday.

"You are the bows from which your children as living arrows are sent forth.

"For even as He loves the arrow that flies, so He loves also the bow that is stable."

In the midst of change let us again be schizoid—like the bow—both flexible and stable. Let us be ministers of *both* art and science in our care of the "whole patient."

E. Tremain Bradley, m.d.

FROM THE GENERAL MANAGER'S OFFICE

William R. Richards, m.d., *General Manager*
160 St. Ronan Street, New Haven, Conn.
Telephone 865 0587

Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

SUMMARY OF ACTIONS COUNCIL MEETING

Thursday, June 15, 1967

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Bradley, Grendon, Polivy, H. Caplan, M. Caplan, Fabro, Hess, Rogol, Cramer, Abbot, Spitz, Hastings, Shepard, Ayres, Jacobson, Jr., Johnson, Grant, Petrie, Palomba, Roch, and Pelz. Also present were: Mrs. Lindquist, Mr. Chilcoat (AMA), Mr. Norbeck (AMA) and Dr. Richards.

Absent were: Drs. Gardner, Brandon, Egan, Nolan and Wilson; also Mr. Villano.

II. Routine Business

Introductions

The Chairman introduced Dr. Carl W. Johnson, new Associate Councilor from HCMA, and Mr. Tim Norbeck, AMA Field Representative, who will replace Mr. Chilcoat as representative to Connecticut in the near future. The Council expressed thanks to Mr. Chilcoat for the excellence of his services while assigned to the Society.

Approval Of Minutes

As printed and distributed, it was VOTED to approve the minutes of the meeting of May 17, 1967.

Life Membership

It was VOTED to approve applications for Life Memberships received from the following eligible Active Members:

Ernest Mylon, New Haven (NHCMA)—1967
Thomas J. Danaher, Torrington, (LCMA)—1968

CSMS Dues Exemptions

It was VOTED to grant exemptions from payment of CSMS membership dues to the following Active Members, for the period and reason indicated:

Jules White, New Haven (NHCMA)—Military Service—1967

James S. Harrop, Simsbury (TCMA)—Military Service—1967

Committee Appointments, Resignations, Etc.

(a) It was VOTED to accept, with regret and thanks, the resignation of Walter J. Keefe, Hartford, as a member of the Conference Committee with the Connecticut Pharmaceutical Association. Dr. Keefe is moving to California. It was further VOTED to appoint William F. Van Eck, East Haven, to replace Dr. Keefe on this Conference Committee for the balance of 1967-68.

(b) It was VOTED to appoint Lavius A. Robinson, Danielson, to membership on the Conference Committee with the Connecticut Bar Association, to represent the Windham County area.

(c) It was VOTED to recommend to Governor Dempsey, for reappointment to a new five year term on the State Board of Examiners for Physical Therapists, the name of Thomas F. Hines, Wallingford.

(d) It was VOTED to reappoint Robert S. Mc Knight, Hartford, as CSMS representative to (and member of) the Corporation of Connecticut Postgraduate Seminar in Psychiatry and Neurology. A report on the activities of the CCPSPN was submitted by Dr. McKnight, and this will be reproduced and distributed with the agenda for the next Council meeting.

Reports Of Delegates To Other State Medical Societies

(a) It was VOTED to accept the report submitted by E. Tremain Bradley, CSMS Delegate to the Medical Society of New Jersey, on his attendance at the 201st Annual Meeting of the MSNJ, Atlantic City, May, 1967.

(b) It was VOTED to accept the report submitted by E. Tremain Bradley, CSMS Delegate to the Massachusetts Medical Society, on his attendance at the 186th Annual Meeting of MMS, Boston, May, 1967. It was further VOTED to table indefinitely a motion to distribute copies of the report to the Committee on Hospitals, directing attention to those portions which deal with resolution of physician-hospital disagreements.

Date Of Next Meeting

It was VOTED to request the Chairman, in consulation with the General Manager, to call the next meeting whenever there is sufficient business to be acted upon. To maintain agreed upon rotation of weekdays, the meeting should be called for a Wednesday.

III. Old, New And Special Business

Minutes—Liaison Meeting With CG On Medicare B

It was VOTED to accept the minutes of the May 15 Liaison Meeting, as printed and distributed, noting that the presence of Dr. Richards at the meeting had not been recorded. Pursuant to these minutes, a general discussion was held as to the most appropriate day and time for holding the Educational Seminar on Review Committees recommended jointly by CSMS and CG representatives. It was VOTED to hold the Seminar in the evening, starting at 7:00 P.M., on either Wednesday or Thursday of the week of July 10 (Thursday, July 13 has been selected) at the Yankee Silversmith Inn, Wallingford. It was VOTED to extend invitations to *all* members of county medical association review committees (instead of just the chairman and one member) as well as to the CSMS Committee on Third Party Payments.

Report—Conference Committee With Conneticut Pharmaceutical Association

It was VOTED to accept a report of the Conference Committee with CPA as information, the report being concerned with the practice of physicians furnishing pharmacists with pre-signed prescription blanks in order to facilitate the telephone prescribing of drugs, both narcotic and non-narcotic. In brief, the report indicated that several pharmacists had been penalized by the Pharmacy Commission for participating in this practice, and recommended that the Council find the practice to be "unprofessional conduct," widely publicize this finding among the membership, and urge all physicians to refrain from such practice. It was further VOTED to carry out such publicity by requesting the county associations having newsletters to report this finding of "unprofessional conduct" in their publications, and to make special note of same in *Connecticut Medicine.*

Report—Committee On Postgraduate Education

In a special report to the Council, the Committee on Postgraduate Education reaffirmed its previous (Council-approved) recommendation that a Clinical Congress *not* be held in 1967, and further recommended that a Clinical Congress *not* be held in 1968 as well. It was VOTED to adopt this latter recommendation of the Committee. It was further VOTED to accept the report, and to approve 5 other recommendations contained therein concerning future activities of the Committee in the field of postgraduate education and to authorize the Committee to implement these proposals. Finally, it was VOTED to direct the staff to prepare an amendment to the bylaws (as recommended by the Committee) so that reference to the Clinical Congress as an annual meeting of the Society will be deleted. In the discussion that preceded this action, it was pointed out that such an amendment would not preclude the Committee on Postgraduate Education from conducting future Clinical Congresses, if it were felt desirable to do so; i.e., the amendment would only make it not *mandatory* that a Clinical Congress be "arranged and conducted" for members of the Society.

Report—Fiscal Advisory Committee

The Council's FAC made recommendations on three fiscal matters which were acted on as follows:

(a) It was VOTED to approve the FAC's recommendation that the sum of $75 be allocated to the Committee on Preliminary Study of Censorship Questions to be used to defray expenses incurred by the Committee's statewide study of the bylaws of hospital medical staffs.

(b) It was VOTED to approve the FAC's recommendation that the sum of $140 be appropriated out of the general funds to cover the costs of publishing an article titled: "Advising Your Patients About the Social Security Disability Program" as a supplement to the Journal.

(c) It was VOTED to disapprove the FAC's recommendation that a Delegate to the Connecticut Nutrition Council be reimbursed for partial expenses incurred in attending a recent meeting of the CNC, but to inform the Delegate that while it is not present policy to reimburse such delegates for such expenses, the Council will review the policy concerning expense reimbursements to *all* committees, representatives, delegates, etc., and will make recommendations concerning same to the 1967 semiannual meeting of the House of Delegates when the budget for 1968 is submitted.

Report—Ad Hoc Committee On PR Director's Employment

E. Tremain Bradley, Chairman of the Ad Hoc Committee, filed a report which recommended that Mr. Villano be offered a five-year contract with the Society at a starting annual salary known to be bilaterally satisfactory. It was VOTED to approve the report of the Ad Hoc Committee, and to implement the recommendation retroactive to June 1, 1967.

Appointment—Ad Hoc Committee On Employment Of Assistant General Manager

It was VOTED to request the Chairman to appoint an Ad Hoc Committee to study and make recommendations to the Council concerning the need for, desirability of, requirements for, etc. establishing the post of Assistant General Manager. Dr. S. J. Martin appointed the Ad Hoc Committee as follows: E. Tremain Bradley, Chairman; Drs. Grendon, Polivy, Abbot, Shepard, and Rogol (FAC members); Dr. Celentano; Dr. Hess, Councilor-at-

Large; and Dr. Richards, General Manager. ex-officio.

Compac

It was VOTED to receive as information several communications from the Board of Directors of the Connecticut Medical Political Action Committee to members of the Council. In brief, the communications listed a number of activities in which COMPAC had engaged in recent months, including a comprehensive report on the AMPAC National Workshop, Washington, D.C., June 2-3-4, 1967. It was reported that the members of the CSMS COMPAC Liaison Committee (appointed May 17) will be invited to attend the next meeting of the Board of Directors to discuss ways and means of establishing improved continuing communications between the Council and the COMPAC Board.

Report—On State Legislation, 1967

Isadore H. Friedberg, Chairman of the Legislative Division and of the Committee on State Legislation, had been invited to join the Council at this meeting to present a "wrap-up" on the measures the Society supported and opposed at the just-concluded session of the General Assembly, and to submit an evaluation of the effectiveness of the Committee, legislative agent, staff, etc. in carrying on the legislative program. However, due to a death in his family, Dr. Friedberg was unable to attend this meeting and will plan to make his report in person at the next one. In lieu of Dr. Friedberg's definitive report, the Council members received a summary of legislation in which the Society had an interest which had been prepared by the Public Relations Director. Pursuant to a discussion of these matters, it was VOTED that, pending receipt of Dr. Friedberg's report and Council approval thereof, no new agreements or renewal of existing agreements be entered into with agencies or individuals rendering services to the Society in the legislative field (legislative reporting service, legislative agent, etc.).

The New Title XIX (Medicaid) Program

Having been apprised of the provisions of the statute enacted by the 1967 General Assembly governing the payment of physicians for services rendered to beneficiaries of Title XIX Medicaid, the Council took the following actions:

(a) Since the statute provides that between October 1, 1967 and March 1, 1968, physicians will be paid for their services in accordance with a uniform fee schedule, it was VOTED to direct the Advisory Committee to the State Commissioners of Welfare, Finance and Control to seek a meeting with the Commissioners forthwith to obtain full information as to how the uniform fee schedule will be arrived at and what claims procedure is to be followed by doctors of medicine prior to March 1, 1968 (when use of the "usual and customary charge" method will be instituted for doctors of medicine *only*).

(b) Since the statute provides that, from March 1, 1968 to March 1, 1969, the "usual and customary charge" method of payment for physicians' services will be in effect, and that a Medical Advisory Committee of not fewer than twenty members (a majority of which are to be doctors of medicine nominated by the Connecticut State Medical Society) will be appointed by the Commissioner of Welfare prior to March 1, 1968, it was VOTED to request the President and Chairman of the Council to compile a list of at least twenty qualified members of the Society to submit to the Council for approval as nominees to be furnished to the Commissioner for appointment to said Medical Advisory Committee. It is understood that, in compiling the list, proper regard is to be given to types of practice, geographic location, etc. of the CSMS members selected by Drs. Bradley and Martin.

Informational Report—Dependents' Medical Care Program

Received as information was a report by the General Manager that, in a copy of a June 8 letter addressed to Dr. William Horton of CMS, Inc. (fiscal agent for DMCP), the Executive Director of ODMC stated that the Defense Department has made two recent rulings as follows: "(I) That in those states where no contracts exist with state medical societies, the "usual, customary and reasonable" fee concept developed by the Social Security Administration in implementing the Social Security Amendments of 1965 should be followed; and (2), that in each state where a contract exists with a state medical society prescribing local schedules of allowances, the policy specified in (1) should be implemented effective upon the termination of the present contract." The letter concludes: "As there is little time remaining until the end of the current contract (July 31), I would appreciate your comments (with reference to the method and procedures you might employ in effecting this . . . concept) at your earliest convenience." The Society is still awaiting word from ODMC that a "usual and customary" agreement has been developed for evaluation and possible approval before July 31.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on June 15, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

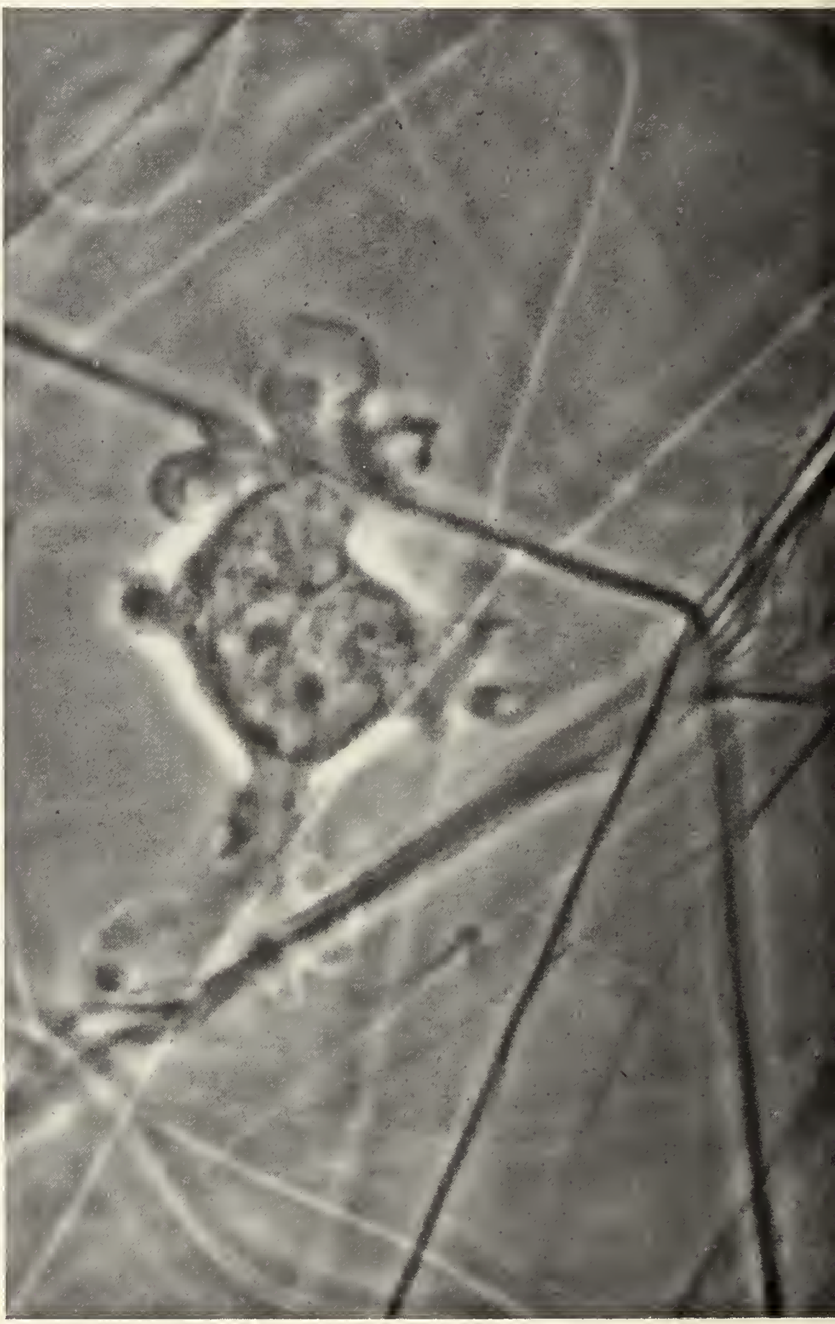
INFLAMMATION:

A cellular fight for life

A SYNTEX REPORT based on recently developed hypotheses about topical corticosteroids, including the cellular theories of inflammation by Thomas F. Dougherty, Ph.D., University of Utah.

You are looking at a fibroblast fighting for life. This cell – one of the most common found in connective tissue – has literally been poisoned by cytotoxins released from other cells that have ruptured. Soon, if the abnormal activity of this fibroblast does not cease, it, too, will rupture and die – one more casualty in the inflammatory wave of destruction precipitated by injury.

Until a short time ago no one had ever witnessed such a scene at the cellular level. Now, through advanced cinemicrographic techniques, it is possible to view and photograph the inflammatory process as produced experimentally in living animal tissue. This method permits new insight into the mechanism of inflammation and the role of corticosteroids in therapeutic management. Equally important, these techniques shed new light on factors that may make one corticosteroid more effective than another – factors that can be correlated with other chemical, biologic, and clinical parameters.



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Contact Dermatitis	27	750	713
Eczematous Dermatitis	21	472	409
Seborrheic Dermatitis	18	442	426
Atopic Dermatitis	24	460	426
Psoriasis	36	1,699	1,510
Neurodermatitis	18	351	324
Total	144	4,174	3,808

*Complete bibliography on request.

†Expressed by the authors as excellent, very good, good, complete remission of inflammation, etc.

PRESCRIBING INFORMATION

For initiation of therapy: Cream 0.025%, 5 and 15 Gm. tubes, 425 Gm. jars; *for emollient effect:* Ointment 0.025%, 15 Gm. tubes; *for maintenance therapy:* Cream 0.01%, 15 and 45 Gm. tubes, 120 Gm. jars; *for intertriginous or hairy sites:* Solution 0.01%, 20 cc. and 60 cc. plastic squeeze bottles; *for infected inflammatory dermatoses:* Neo-Synalar® Cream (0.025% fluocinolone acetonide, neomycin sulfate, equivalent to 0.35% neomycin base), 5 and 15 Gm. tubes. CONTRAINDICATIONS: Tuberculous, fungal, and most viral lesions of the skin, (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. PRECAUTIONS: Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Prolonged use of any antibiotic may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy should be instituted. When severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. SIDE EFFECTS: Side effects are not ordinarily encountered with topically applied corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. The neomycin in Neo-Synalar Cream rarely produces allergic reactions.

REFERENCES: 1. Lerner, L. J., Bianchi, A., Turkheimer, A. R., Singer, F. M., and Borman, A.: Anti-inflammatory steroids: potency, duration and modification of activities. Ann NY Acad Sci 116:1071 (Aug. 27) 1964. 2. Idem: Comparison of anti-granuloma, thymolytic and glucocorticoid activities of anti-inflammatory steroids. Proc Soc Exp Biol Med 116:385 (June) 1964. 3. Ringler, A.: Activities of adrenocorticosteroids in experimental animals and man, in Dorfman, R. I.: Methods of hormone research, New York, Academic Press, 1964. vol. III. pp. 234-280. 4. Gubersky, V. R.: To be published.

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A.M.A. Takes Position On Staff Appointments

The principle of a resolution introduced by the Connecticut delegation calling for an "open" policy with regard to hospital staff appointments was adopted by the AMA House of Delegates at the 116th Annual Convention.

The resolution, previously adopted by The Council and House of Delegates of the Connecticut State Medical Society, noted that a double standard of policy often exists between so-called "hospital-based specialists" and other types of practitioners with respect to such appointments.

As amended in Reference Committee and finally adopted, the resolution places the AMA behind "the principle of a single standard with respect to staff appointments among all physicians having equivalent credentials in all hospital departments and services as a means of assuring maximum freedom of choice of physicians by patients, and of consultants by staff members."

The adoption of a single standard does not, however, preclude "effective departmental organization and appropriate delegation of authority and responsibility."

The House of Delegates urged constituent state and component county units "to bring this endorsement to the attention of the medical staffs and governing authorities of all hospitals operating within their jurisdictions. . . ."

PLACEMENT WANTED

SURGEON—35 years of age, Board certified, presently completing military obligations. Would like to practice with a group or an associate in a medium to small community.

SURGEON—37 years of age, Board eligible, wishes to practice with a group or an associate in a medium-sized community.

SURGEON—Board certified, military obligations completed. Wishes to practice in a medium to small community in a solo or associate situation. Available immediately.

ANESTHESIOLOGIST—Board eligible, with residency in Internal Medicine. Wishes to practice in a small community in a solo or associate practice. Available immediately.

G.P.—49 years of age, applied for Connecticut license. Would like to practice in a larger to medium-sized community in a group or associate practice.

INTERNIST—43 years of age, Board eligible. Wishes to practice with a group or an individual, excellent background training in Cardiology. Connecticut license.

PLACEMENT OPPORTUNITIES

PEDIATRICIAN—Pediatrician to associate with two established pediatricians in Southern Connecticut costal town. Liberal salary first year, then partnership.

PHYSICIAN—with background in internal medicine and/or pediatrics who is interested in a group practice in a rural town in Southern Connecticut. Hospital services available at several area hospitals.

INTERNIST—Board certified or eligible, military obligations completed. Three year partnership offered in a Southern Connecticut town.

G.P.—for association with another physician in a well-established practice in a growing industrial city in Southern Connecticut. Partnership possible after one year.

OCCUPATIONAL PHYSICIAN— to associate with 2 other physicians and a staff of 9 nurses, 2 safety engineers, 1 x-ray laboratory technician, part-time optician and a clerical staff in a modern, fully equipped Occupational Medical Department in Central Connecticut. Duties of Occupational Physician involve a program of prevention and treatment of occupational injuries, illnesses and a continuous program of employee health evaluation, beginning with job preplacement examination. Emphasis placed on medical evaluation of the employee with particular reference to physical demands and environmental exposures of his individual job, and participation in employee health counseling, periodic examination programs and evaluation of environmental exposure factors for employee health and safety.

A program of indoctrination will be conducted for the new physician. Work schedule consists of 5 days a week and no obligation to be on call nights or weekends. Outside practice permitted if it does not interfere with regular duties, and he will enjoy an excellent relationship with local practitioners, consultants and hospitals in the Hartford-Springfield areas. Salary commensurate with individual's experience. Write or call: 623-1621, Dr. Lawrence Coleman, Hamilton Standard, Bradley Field Road, Windsor Locks, Connecticut 06096.

MEDICAL DIRECTOR—a leading industrial firm needs a top man, Board qualified in internal medicine or occupational health. Will deal with various industrial health problems and supervise a staff. Responsible for planning and implementing new programs. Most likely will have clinical or industrial experience. This man may come from a university, hospital research group, private practice or government projects. Headquarters, New England, Top company and conditions. Salary to $35,000. Contact: Richard P. Rita Personnel, 993

Farmington Avenue, West Hartford, 263-3249, with resume.

FULL TIME Health Director needed for brand new regional health district in picturesque Connecticut. Handy to fine schools, colleges, Berkshire mountains, salt water, skiing, golfing, music centers, etc. Salary $18,500 per annum. Apply to Fowler White, M.D., Acting Director; Torrington Regional Health District, 59 Field Street, Torrington, Connecticut 06790 or phone 203-482-4441.

MEDICAL DIRECTOR — Full time Medical Director for the Child Guidance Clinic for Central Connecticut, Inc. Board certification is not required. Experience with child psychiatry preferred. Regular hours. Qualified staff. Progressive mental health community. Salary $18,000-$25,000, with excellent fringe benefits. Contact Mrs. B. H. Hunt, Personnel Chairman, Child Guidance Clinic for Central Connecticut, Inc., 116 Lincoln Street, Meriden, Conn. 06450.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN ST., NEW HAVEN, CONNECTICUT 06511.

1967 Meetings

September 27—175th Semi-annual meeting of the Hartford County Medical Association will be held at the Hartford-Hilton Hotel, Hartford. Business meeting starting at 5 P.M. and dinner at approximately 7 p.m.

October 26—Semi-Annual meeting of the New Haven County Medical Association to be held at Waverly Inn, Cheshire, Conn., beginning at 3:30 p.m.

1968 Meetings

April 30, May 1-2—176th Annaul Meeting of the Connecticut Medical Society to be held at the Hartford-Hilton Hotel, Hartford, Connecticut.

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Ophthalmologist Outlines Technique

When a cataract began to form in the eye of a 67-year-old woman, she blamed its formation on a drug which she had taken and discontinued several years previously.

Although the drug is known to be associated with cataract formation on occasion, a Northwestern University ophthalmologist was able to prove that in this instance it was innocent.

Using the techniques of a new ophthalmological field of study which he calls phakochronology, John G. Bellows, M.D., Ph.D., found that the cataract had started to form about two years after the drug was discontinued.

Appearing here at the scientific session of the American Medical Association's 116th Annual Convention, Dr. Bellows described his work with this and other cases.

Phakochronology is the science of determining the age of disturbances that leave permanent imprints on the crystalline lens of the eye.

The crystalline lens of the eye is the only part of the body that can be studied as a botanist studies a tree's annular rings, explained Dr. Bellows, Northwestern University School of Medicine, Chicago.

Accurate dating of alterations in the lens, he said, can assist the ophthalmologist in determining whether the changes are recent and progressive or older and relatively inactive. Age determinations may also have medico-legal implications as in the case of the woman who thought a drug had caused a cataract.

He noted that ophthalmologists make such determinations now in lens examinations, but more or less roughly and by rule of thumb. He urged more study and the refining of techniques for more accurate measurements.

Phakochronology (derived from the Greek phokos—lens, and chronos—time) is actually a study of the lens as a recording chronometer.

The crystalline lens forms before birth and continues to grow as long as the body lives. During intra-uterine life the lens may be damaged by infectious, toxic, metabolic and endocrine diseases in the mother. After birth, damage may be caused by local or systemic infections, poisons, injuries, metabolic disturbances, sunlight, and ionizing radiation.

It is the growth pattern of the lens which marks its singularity as a tissue.

As it grows, the lens incorporates its old cells rather than casting them off. Each newly-formed lens fiber compresses the lens fiber underlying it; when enough fibers are compressed, they form a layer which, by its index of refraction, is distinguished from preceding and succeeding layers.

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Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should be closely supervised and should be warned to report immediately fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage. Make regular blood counts. Discontinue the drug and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. Infrequently, agranulocytosis, or a generalized allergic reaction may occur and require withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported but cannot definitely be attributed to the drug. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Painful Shoulder: 600 mg. daily in divided doses for 2 to 3 days; 300 mg. daily thereafter. Usual duration of therapy: 2 to 7 days.

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THE PRE-SIGNING OF PRESCRIPTION BLANKS

Practice Ruled to be "Unprofessional Conduct"

In recent months concerned agencies of the State have investigated several instances in which pharmacists had possession of pads of prescription blanks pre-signed by physicians which had been furnished to them by the physicians whose names appeared on the blanks. Representations were made, both by the pharmacists and the physicians, that this arrangement offered several conveniences: (a) That after-hours telephone prescribing by the physician was expedited, for narcotics as well as for non-narcotics, and often was an accommodation to patients, and (b) that time was saved for the physician in instances where duplicate prescription forms were required (such as for welfare cases).

These situations came to the attention of the authorities as a consequence of the use of the pre-signed blanks by several pharmacists to cover telephoned orders for dispensing Class A narcotics received from physicians, a practice ruled to be contrary to regulations. However, the Joint Conference Committee of the Society with the Connecticut Pharmaceutical Association has reported the opinion to the Council that the practice is equally unprofessional when non-narcotic drugs and/or expediency are involved.

On June 15, 1967, the Council approved this report of the Conference Committee and ruled that the practice of furnishing pre-signed prescription blanks to pharmacists for any purpose constitutes "unprofessional conduct" on the part of physicians and is one to be avoided at all times.

In response to an inquiry as to whether such practice may also be "illegal," State Health Commissioner Franklin M. Foote has stated: It (the practice) would provide the opportunity for serious problems, as is evidenced by reports coming in from several of our investigators. These reports disclose the fact that, in some instances, pads of such prescriptions have been found readily available to persons other than the pharmacists. Because this practice is potentially so fraught with danger, we feel it to be most improper and might subject any physician engaging in it to being called before the Connecticut Medical Examining Board to determine whether his license should be suspended on charges of "unprofessional conduct."

A WORD TO THE WISE SHOULD BE SUFFICIENT.

WOMAN'S AUXILIARY

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ROUND-UP REPORT OF THE 44TH ANNUAL CONVENTION OF THE WOMAN'S AUXILIARY TO THE AMA

JUNE 18-22, 1967

CHICAGO, ILLINOIS

A visit from two Vietnamese students, a talk by a noted proponent of sex education and a "Little Workshop" for state presidents and presidents-elect were outsanding features of the 44th annual convention of the Woman's Auxiliary to the American Medical Association. The meeting, held at Atlantic City's Shelburne Hotel, June 18-22, attracted a registration of 1,052 physicians' wives.

Auxiliary President Mrs. Asher Yaguda presided over the sessions. The Vietnamese students, both mothers of three-year-old daughters, visited the convention on Monday and were available to meet their auxiliary sponsors. The two young women were "adopted" by the auxiliary for their short-term, specialized medical training at the Georgetown University School of Medicine in Washington, D.C. Part of their living expenses for their three-month training, is being paid for by auxiliary sponsors.

Dr. Mary S. Calderone, director of the Sex Information and Education Council of the United States, spoke during the Tuesday morning session on "Sex Education: Goals and Means." Other speakers included Anne R. Somers, research associate, industrial relations section, Princeton University; and Charles L. Hudson, M.D., 1966-67 AMA president, who spoke on "The Women—Bless 'Em" during the annual luncheon honoring auxiliary past presidents and AMA officers, trustees and their wives.

A highlight of the convention was the "Little Workshop," a two-way discussion led by national committee chairmen on auxiliary programs.

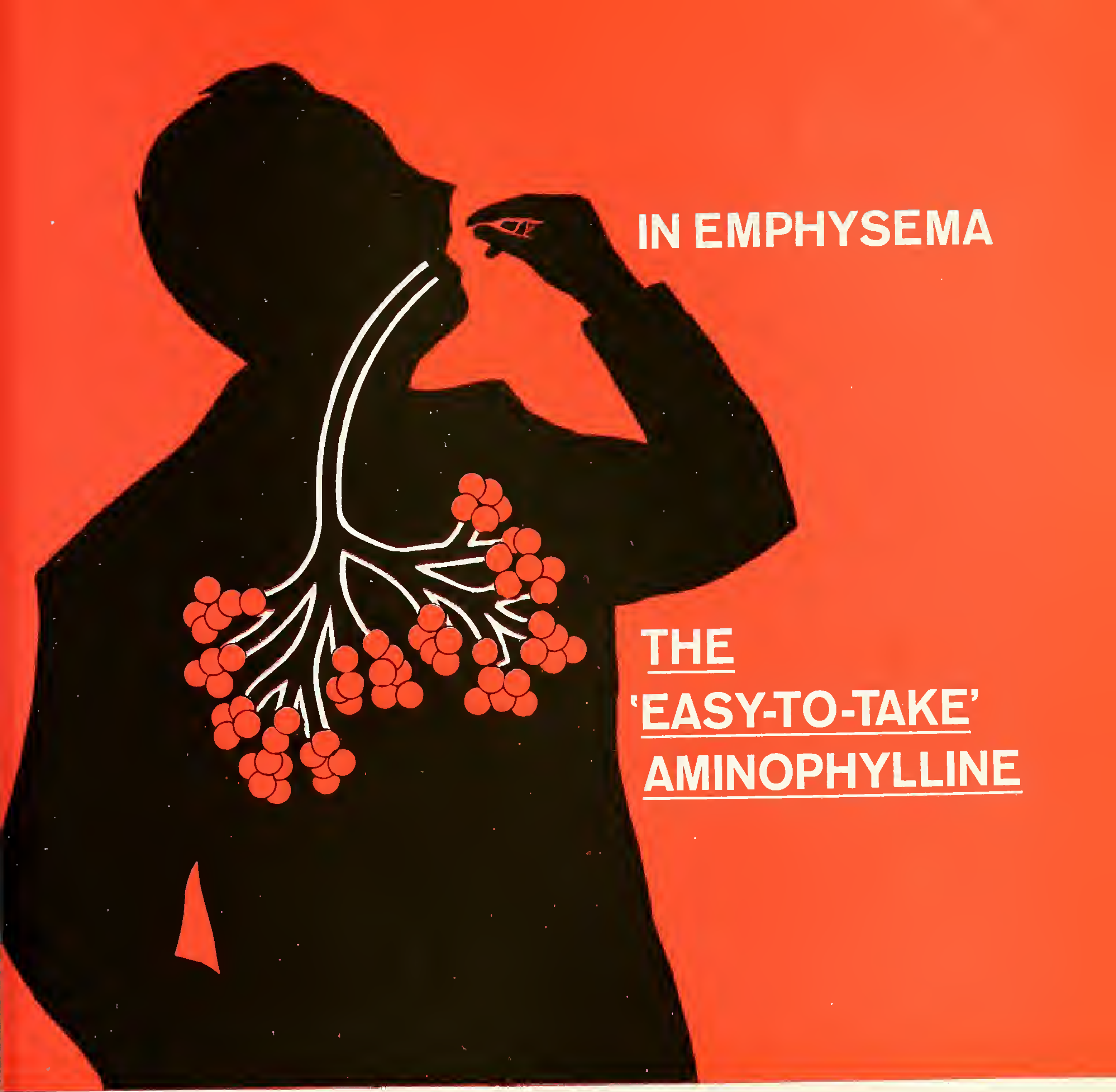
The auxiliary's annual contribution to the AMA Education and Research Foundation—this year amounting to $384,649.48—was presented during the convention. Six state auxiliaries receiving awards of merit for raising the largest amounts in their membership categories were Wyoming, Maryland, West Virginia, Tennessee, Indiana and California.

Miss Margaret Wolfe, executive secretary of the auxiliary, was made an honorary member of the organization in recognition of 25 years of service in her position.

Other convention highlights were the presentation of the Health Mobilization Award to the Robeson County, N.C., auxiliary for its work in training citizens in medical self-help; and a Sunday evening reception honoring Mrs. Yaguda and Mrs. Karl F. Ritter, president-elect.

Mrs. Ritter presented her inagural address on Wednesday, June 21, following her installation as president. Present for the occasion were Dr. Milford O. Rouse, newly installed AMA president, and Mrs. Rouse.

Other officers installed were Mrs. C. C. Long, Ozark, Ark., president-elect; Mrs. Howard Liljestrand, Honolulu, Hawaii, first vice president; Mrs. Robert F. Beckley, Lock Haven, Penn. Eastern regional vice president; Mrs. John D. Dickie, Toledo, Ohio, North Central vice president; Mrs. R. C. L. Robertson, Houston, Tex., Southern regional vice president; Mrs. Clare W. Johnson, Phoenix, Arizona, Western regional vice president; Mrs. Erle E. Wilkinson, Nashville, Tenn., constitutional secretary; Mrs. E. R. W. Fox, Coeur d'Alene, Idaho, treasurer; and directors, Mrs. George W. Gasser, Logan, Utah; Mrs. J. Murray Kinsman, Louisville, Ky.; Mrs. Jost J. Michelsen, Boston, Mass.; Mrs. Paul E. Rauschenbach, Paterson, N.J.; Mrs. Willard C. Scrivner, East St. Louis, Ill., and Mrs. Herbert J. Ulrich, Buffalo, N.Y.



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Serving their second year as directors are Mrs. Thomas Anton, Mrs. Norman H. Gardner, Mrs. Amos N. Johnson, Mrs. Burton E. Kintner, Mrs. W. A. Merritt and Mrs. Glenn T. Scott.

Additional convention features were:

- The Monday Guest Day Luncheon for representatives of national women's organizations.
- The Monday Family Night for auxiliary and AMA members, guests, children and teenagers.
- Reports from state auxiliary presidents.
- A political action discussion by Miss Evelyn Dubrow, legislative representative, International Ladies' Garment Workers' Union and Miss Lee Ann Elliott, assistant director, AMPAC.
- A round-up report on the AMA House of Delegates activities by Ernest B. Howard, M.D., AMA assistant executive vice president.
- A report of the AMA's activities in home-centered health care by Roy F. Perkins, M.D., director, AMA Department of Health Care Services.

Special Notice

CARDIAC SYMPOSIUM

Sponsored by the Northwest Chapter of the Connecticut Heart Association

and the

Graduate Education Department of St. Mary's Hospital Waterbury

October 12, 1967

To be held at St. Mary's Hospital, Waterbury, Connecticut at the Nurses' Auditorium

PROGRAM

9:30-10:00	Official Registration
10:00-10:45	"Management and Evaluation of Coronary Care Units" by Dr. Victor Keyloun, St. Vincent's Hospital, New York City.
10:45-11:30	"Treatment of Shock and Other Complications in Acute Myocardial Infarction" by Dr. Leslie Kuhn, Associate Clinical Professor, the Mount Sinai Hospital School of Medicine; Associate Editor of the *American Journal of Cardiology*.
11:30-12:15	"Course and Medical Management of Coronary Heart Disease" by Dr. Harry Jaffe.
12:30	LUNCH
1:30- 2:30	"Surgical Treatment of Coronary Heart Disease" by Dr. William H. Sewell, Jr., Chief of Cardiac Surgery, Guthrie Clinic, Sayre, Pennsylvania and author of "Surgery for Acquired Coronary Disease."
2:30- 3:30	Panel Discussion of Problems in Coronary Heart Disease (Questions solicited from the floor) Harry Jaffe, M.D., Victor Keyloun, M.D., Leslie Kuhn, M.D., William H. Sewell, Jr., M.D.

A tour of our Coronary Care Unit at St. Mary's Hospital will be the end point of the program.

BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Synopsis of Pediatrics. Second Edition. Edited by James G. Hughes, B.A., M.D. The C. V. Mosby Company, Saint Louis, 1967. 1099 pp. with 86 illustrations, $10.85.

A Textbook for Medical Assistants. Edited by M. Murray Lawton, M.D. and Donald F. Foy, B.S., M.S. The C. V. Mosby Company, Saint Louis, 1967. 465 pp. $8.85.

It All Started with Hippocrates. Edited by Richard Armour with illustrations by Campbell Grant. McGraw-Hill Book Company, New York, Toronto, London and Sydney, 1967. 136 pp. $3.95.

Lectures to Relatives of Former Patients. Edited by Abraham A. Low, M.D., Founder of Recovery, Inc. The Christopher Publishing House, Boston, U.S.A., 1967. 229 pp. $5.00.

New Drugs. 1967 Edition. Evaluated by A.M.A. Council On Drugs. American Medical Association, Chicago, 1967. 590 pp.

Clinical Judgment. Edited by Alvan R. Feinstein, M.D. The Williams & Wilkins Company, Baltimore, 1967. 414 pp. $9.50.

Pathologic Physiology—Mechanisms of Disease. Fourth Edition. Edited by William A. Sodeman, M.D., Sc.D., F.A.C.P. and William A. Sodeman, Jr., M.D. W. B. Saunders Company, Philadelphia and London, 1967. Illustrated, 1051 pp. $19.00.

Effects of External Stimuli on Reproduction. Ciba Foundation Study Group No. 26. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1967. 107 pp. with 10 illustrations.

Mongolism. Ciba Foundation Study Group No. 25. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Ruth Porter, M.R.C.P. Little, Brown and Company, Boston, 1967. 99 pp. with 23 illustrations.

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OBITUARY

Timothy F. Brewer, M.D.

1901-1967

Dr. Timothy Brewer died at his home in West Hartford, Connecticut on May 31, 1967 after a long disabling illness.

Born in Norwich, Connecticut he graduated from Norwich Free Academy, obtained his A.B. degree from Yale College and in 1926 his M.D. degree from Yale Medical School.

After his internship at New York Hospital, New York City and residency at St. Francis Hospital, Hartford, Connecticut, he had special training in Cardiology under Dr. Samuel Levine at the Peter Bent-Brigham Hospital, Boston, Massachusetts.

After completing this post graduate special training he was appointed to the medical staff at St. Francis Hospital, Hartford, Connecticut. Sometime later he was also appointed to the medical staff at McCook Memorial Hospital, Hartford, Connecticut. In these institutions he applied his great talents with ceaseless dedication, much to the admiration of his colleagues and patients.

In October 1940 he served as Examining Physician in the Selective Service System while carrying on his private practice and hospital duties until the local needs were less pressing: Then he volunteered for active duty in the Medical Corps of the U.S. Navy in response to the urgent need for medical officers. He entered the Navy and served as a Lt. Commander in California and the Pacific until released from active duty in October 1946.

"Well Done" connotes the performance of his medical duties in civil life as it did in the Navy. He returned to Hartford, Connecticut and resumed practice with the same enthusiasm as previously demonstrated until he developed a disabling illness which ulitmately compelled retirement. He lived happily at home and enjoyed the company of his grandchildren.

He is survived by his wife, Catherine Sullivan Brewer, a son, Dr. Timothy Brewer III, five grandchildren.

Dr. Brewer was a member of the Hartford Medical Society, the Hartford County Medical Association, the Connecticut State Medical Society and the A.M.A. He was a Fellow of the American College of Physicians.

ARTHUR B. LANDRY SR., M.D.

In Memoriam

Douglass, Wallace C.—St. Petersburg, Florida; Long Island College Hospital, 1908. Dr. Douglass was an allergy specialist for many years. He was a member of the Connecticut State Medical Society and the American Medical Association. He was an Associate Fellow of the American College of Allergists. Dr. Douglass died December 17, 1966, at the age of 83.

Pennington, Harry F.—Meriden; Harvard School of Medicine, 1927. A specialist in obstetrics and gynecology, Dr. Pennington was senior staff attending physician at Meriden Hospital, where he also served as head of the Obstetrical Department in the past. He was chief obstetrics for many years at the Veteran's Memorial Hospital, Meriden. He was a member of the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Pennington was a diplomat of the American Board of Obstetrics and Gynecologists. He served as a member of the Meriden Board of Health from 1938 to 1940. He was a long-standing member of the U.S. Power Squadron, the largest boating organization in the world. Dr. Pennington died July 4, at the age of 65.

Doctor's Office

Charles A Gundersen, M.D., announces the opening of an office for the practice of medicine at 2900 Main Street, Glastonbury.

Brian C. Hennessey, M.D., announces the opening of an office for the practice of obstetrics and gynecology at 88 Goodwin Street, Bristol.

David B. Hickox, M.D., announces his association with Andrew F. Turano, M.D. in the practice of pediatrics at 33 Pleasant Street, Middletown.

William A. Hoffman, M.D., announces his association with Edwin Hankin, M.D. for the practice of internal medicine and gastroenterology at 1700 Post Road, Fairfield.

Enrique Izurieta, M.D., announces the opening of an office for the practice of internal medicine at 881 Lafayette Street, Bridgeport.

C. P. Noel McCarthy, M.D., announces the opening of an office for the practice of obstetrics and gynecology at 75 Washington Avenue, North Haven.

Willard J. Morse, Jr., M.D. in association with Willard J. Morse, M.D., announces the removal of their office from 32 Channing Street to 290 Pequot Avenue, New London.

NEW BOOKS IN REVIEW

A PRIMER OF ELECTROCARDIOGRAPHY by George E. Burch, M.D., F.A.C.P., and Travis Winsor, M.D., F.A.C.P. Lea & Febiger, Philadelphia, 1966, Fifth edition, 304 pp., 286 illustrations. $6.50.

Reviewed by: LOUIS H. NAHUM

This 5th edition follows the 4th at an interval of six years. The authors state that there have been no great changes in the concepts of the electrocardiogram within the last six years. This is true but there have been fundamental changes in the last twenty years which have yet to find their way into this primer. Mainly they have evolved from applying experimental techniques such as stimulating various areas, heating and cooling and injury to various areas and then following the changes as they appear in the different leads. Such studies have shown that the heart cannot be treated as a single cell, but is in fact a very complicated source of current with much cancellation of potentials from the endocardial and intramyocardial layers leaving these areas relatively silent. The major source of potentials that make up the surface field seem to be derived from the outer third of the myocardial shell.

Another important development is the plotting of the surface field function which has revealed the heart as a highly complex source of current rather than the stylized dipole which formerly dominated the concepts of electrocardiography. The field function studies have dislodged the concept of an electrical axis and have in fact made groundless the assumptions upon which vectorcardiography was based. In this sense the ten pages devoted to vectorcardiography are more than sufficient since this reviewer agrees that this subject has not developed to a point sufficient to justify its use by the clinician.

As a result of these new developments an attempt to explain the electrocardiogram as a consequence of a dipole moving from endocardium to epicardium is brought into serious question. The three stages in healing of an infarct, in figure 177, page 173, does not mention the hyperacute phase. A meaningful analysis of primary and secondary T changes in bundle branch block is also missing. The term "strain" which is a mechanical not an electrical concept is used when what is probably meant is hypertrophy and parietal block. The ventricular gradient is given fourteen precious pages although its usefulness as a diagnostic tool has declined in the last twenty years and especially since Pipberger and his associates have shown how little value it really has.

A brief reference to the ECG changes following exercise in ischemic heart disease could add useful information to the new electrocardiographers. There are however valuable normal standards by age up to twenty years and perhaps the next edition will present similar values for over age thirty, because highly significant changes begin to occur after this age.

The illustrations are beautiful and clear, the nomenclature, measurements and the main types of ECG abnormalities are presented in a clear and understandable manner. The ECG criteria listed in the appendix pages 291 to 295 are useful for systematization of interpretation. Because of these there is little doubt that this new edition as the others will receive wide attention and will be received favorably by the upcoming generation of lectrocardiographers, as have the previous editions.

PRINCIPLES OF BIOMOLECULAR ORGANIZATION. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A., Little, Brown and Company, Boston, 1966. 141 illustrations. 491 pp. $15.00.

Reviewed by: PAUL M. GALLOP

This valuable volume records the record of an international symposium dealing with problems of biomolecular organization. The high caliber of the papers and the stimulating discussions led by the Chairman, Dr. Crick, are essential reading for all molecular biologists, biologists and biochemists. Many new ideas are discussed and particular emphasis is placed on the emergence of general rules which appear to govern the spontaneous organization of more complex biological entities from simpler macromolecules. The contributors to this volume represent some of the leaders in their respective areas of research.

The reviewer enthusiastically recommends this volume.

EGG IMPLANTATION, Ciba Foundation Study Group No. 23, by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A., Little, Brown and Company, Boston, 1966. 25 illustrations, 112 pp.

Reviewed by: LOUIS H. NAHUM

This book is dedicated to Professor R. Courrier on his 70th birthday. The questions asked were how does the uterus know that the blastocyte is where it is? Does the sensitized uterus attract the blastocyte or does the blastocyte stimulate the uterus or what combination of the wo forces lead to successful implantation? There were twenty-six world famous leaders in the field of physiological control of gestation and reproductive physiology, some presenting papers and all participating in the discussion. All in all a good time was had by all. Facts relating to all steps in the process of implantation from the stage of fertilization, through the mechanism of implantation when the implanted egg starts on its job of developing into a fetus, were freely elaborated and argued.

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References: 1. Batterman, R. C., and Grossman, A. J.: Fed. Proc. *14*:316, 1955. 2. Goodman, L. S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Company, 1965, p. 331. 3. Roth, J. L. A., *et al.*: Gastroenterology *44*:146, 1963. 4. Conney, A. H., and Burns, J. J.: J. Pharmacol. Exp. Ther. *128*:340, 1960. 5. Settel, E.: Clin. Med. *6*:1373, 1959. 6. Berman, H. H., *et al.*: Dis. Nerv. Syst. *25*:430, 1964. 7. Darienzo, C.: Ibid., *27*:189, 1966.

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Illustrations should be numbered consecutively and indicated in the text. The number, indication of the top, and the author's name should be attached to the back of each illustration. Legend should be typed, numbered, and attached to each illustration. Photographs should be clear and distinct; drawings should be made in black ink (preferably India ink) on white paper. For half tones, glossy photographs should be submitted. Connecticut Medicine will bear the cost of printing two cuts accompanying manuscripts submitted for publication. The cost of printing more than two cuts must be borne by the author.

NEWS

Our readers are requested to send in items of news, also *marked* copies of newspapers containing matter of interest to physicians. Letters intended for publication should be marked "For Publication." We shall be glad to know the name of the sender in every instance. All copy should be received one month prior to the expected date of publication.

ADVERTISING

All advertising copy of products approved by the Advertising Committee of the State Medical Journal Advertising Bureau of Chicago shall be accepted for publication unless such copy is in conflict with official policies of the Connecticut State Medical Society. Non-Bureau advertisements in this issue have been reviewed and found to comply with the principles of advertising of the State Medical Journal Advertising Bureau, Inc. The acceptance of advertisements does not necessarily imply endorsement of any product or service by Connecticut Medicine.

Material other than original articles should be received not later than the 10th of the month PRECEDING date of issue.

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Reprint orders should be returned at once as the type will be destroyed immediately following publication of the manuscript. The Journal does not stock reprints of the articles published. Requests for individual reprints should be sent to the author.

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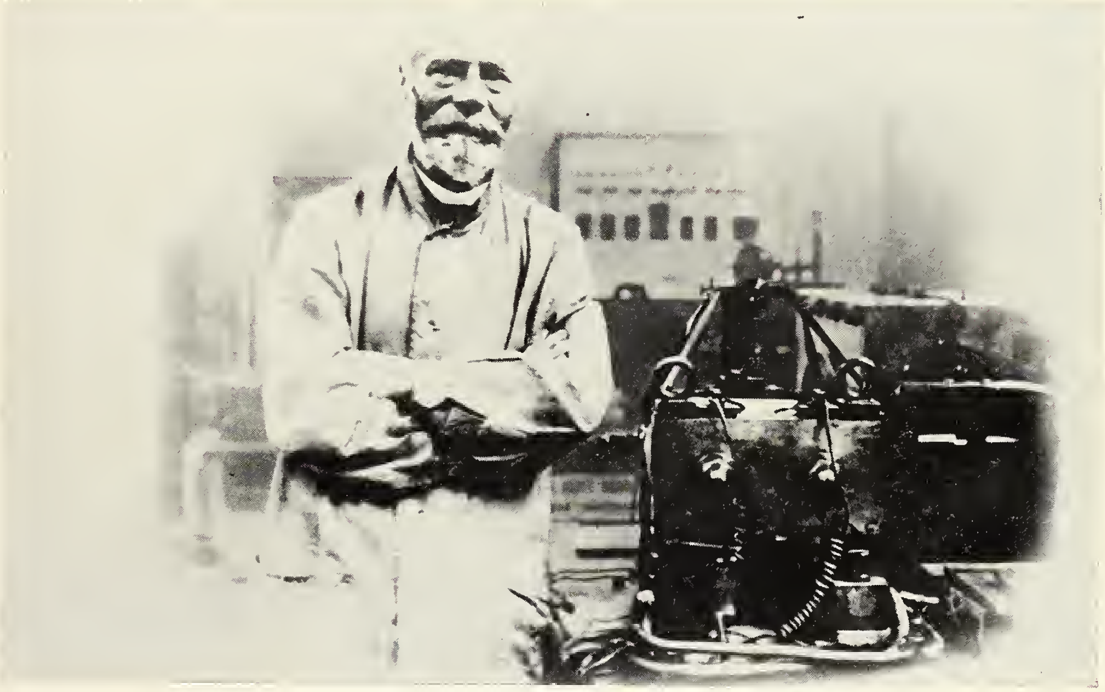
CARDIOVASCULAR DISEASE ISSUE: Allan V. N. Goodyer, M.D., *Guest Editor*



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Connecticut Medicine

editorials

Exercise In Heart Disease. II. Unanswered Questions

The trend to encourage physical training programs today is a wholesome reaction to the previous medical attitudes dominated by the rest dogma.[1] We rarely now see the complete invalidism promoted in the past both physical and psychological although we still occasionally encounter patients surrounded with unbearable "don'ts" and life full of disabling phobias.

The physician in meeting the task of proper management of patients with ischemic heart disease will require a complete evaluation of the patients physical and emotional status from time to time. History and physical examination still form the backbone of this evaluation. How much physical effort produces fatigue, dyspnea, chest discomfort can readily be elicited. Special tests such as exercise tolerance tests can also contribute to a proper classification of the patients capacity to meet extraordinary loads. These may involve measuring the severity and duration of exercise that produce ischemic alterations in the electrocardiogram. Or they may involve an estimate of the pulse and arterial pressure and respiratory changes following several levels of standardized exercise.

Most workers in the field agree that leg exercise carried out in the erect position give the best estimate of the state of the cardiovascular system. Hopping on one foot, climbing steps, bicycle ergometers, treadmills have all been employed in electrocardiographic and hemodynamic evaluation. There is as yet no fully agreed upon method in estimating the duration, intensity of exercise or the criteria to be employed in estimating the effects of exercise upon the heart and blood vessels.

One thing is certain. There are other conditioning maneuvers that need to be carried out at the same time such as weight reduction in the obese, a prudent rather than a gluttonous diet, and discontinuance of cigarette smoking. It is true we will not know what part these play in increasing longevity and how useful training program is by itself. Furthermore even if we attempted to evaluate a training program by itself it could still not eliminate the element of psychology in making a person believe he is becoming better. He may become more motivated to try harder and feel more confident he is getting better. It is very difficult to distinguish between the value of weight reduction, elimination of smoking, diet, exercise or pure ceremony associated with training program in the ultimate benefits to the patient.

We are still waiting for convincing evidence to date that the physical training programs, whether or not combined with other changes in regimen in reality affected morbidity and mortality rates of patients with ischemic heart disease. Even though the final proof for encouraging physical training programs is still pending are there reasons for encouraging them nevertheless?

One question is whether training to improve physical fitness inhibits the basic vascular disease atherosclerosis. We, as Katz[2] points out, have no unequivocal answer to this question. Experiments on animals favor the concept. Epidemiological studies on effect of occupation and mode of life favor the concept. However the evidence that exercise lessens atherogenesis in the presence of an atherogenic regime is equivocal. There are a number of negative reports and there are objections to the design of the studies of some of the positive reports. A wild animal seems to have less atherosclerosis than a tame animal of the same species but we do not know what this is due to, whether it is due to physical fitness, lack of confinement, dietary, genetic or other factors.

Another unanswered question is whether improved physical fitness reduces the morbidity and mortality from coronary artery disease. It has not yet been completely answered. If physical training lessened the occurrence of CAD there would of course be a reduction of the clinical and even the occult manifestation of the disease. Lessened morbidity would tend to lessen mortality. In fact even in the presence of CAD improved physical fitness might alter morbidity if it modified the immediate precipitating causes, such as intravascular thrombosis, platelet adhesiveness, atheromatous ulceration. Can fitness facilitate lysis of thrombi already formed or fibrosis within an atheroma to prevent its development and ultimate rupture. Any one of these might lessen the occurrence of overt clinical manifestations of CAD or lessen the magnitude of the process which damages the heart. We need evidence on this point.

Another question is whether the development of a collateral circulation is hastened by training to the point that it lessens appreciably the coronary insufficiency induced by the coronary occlusive process. Then there must be patients in whom the primary occlusive process outruns the development of collaterals. If the process of collateral developmen can be significantly augmented by training and improved fitness then the severity of the cardiac handicap and the resulting mortality could be reduced significantly. We hope so but we don't know.

The performance capacity of the heart doubtless improves with training. Can this permit the patient to meet better the demands on this pump which otherwise would lead to serious clinical consequences or might even be fatal. We hope so but we don't know.

Is the heart in a physically fit person subjected to a coronary occlusion less prone to fatal arrhythmias than the heart of a less fit person. We don't know but we hope so. Can a trained body respond more efficiently during an acute myocardial infarction so as to help reduce the magnitude of the illness and forestall a fatal outcome. We don't know.

Supposing the training program is nothing more than a "positive approach" to CAD, an approach in which the patient feels that something is being done, in fact an approach in which he himself is doing something constructive to help himself overcome the handicap, real or imagined of this disease and the total effect of the training turns out to be psychological. If so could this be sufficient to justify a training program. The patient is kept aware of his problem not in fear but in an agreeable way. He is more amenable to advice given by his physician who is in this program an interested and constantly available advisor.

The trained patient learns to recognize and report to the physician events that need counsel. Otherwise the patient might ignore or suppress the symptoms and fail to recognize the physician as an interested advisor. This alone would be helpful and morbidity and mortality could be affected.

It is obvious there are as yet no simple yes and no answers as to the value of physical fitness. Keeping the problems in clear focus should certainly lead to more perceptive study and hopefully more positive answers.

L.H.N.

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Exercise In The Physical Examination Of Peripheral Arterial Disease

Arteriosclerotic peripheral arterial disease is prevalent, in many instances disabling, and in fact has received considerable attention both from the point of view of diagnosis as well as therapy. When the lesion involves the lower extremities what is generally emphasized clinically are the classical findings of intermittent claudication, absent pulses, delayed venous filling, pallor of the elevated foot, dependent rubor, and of course ischemic ulcer and gangrene.

However, there are patients, two of which were described by Garrison, Floyd and Orgain[1] in which the diagnosis of peripheral vascular disease was greatly aided by auscultation of the arteries, palpation of the pulses and observation of the skin over the distal part of the extremity both before and after exercise before they could establish the diagnosis of prominent stenosis in the primary arterial supply to the extremity. These simple maneuvers may clearly reveal arterial insufficiency when none or few of the usually emphasized abnormal physical findings are present. The two patients they report had good pulses, one in the leg and the other in the arm, but the one presented with stenosis of the aorta at the bifurcation and of the bilateral iliacs and the other at the subclavian artery.

This emphasized that all patients suspected of peripheral arterial insufficiency should have a physical examination which includes auscultation of accessible arteries, palpation of all pulses and notation of the color of the skin over the distal part of the extremity and this examination should be performed both before and after exercise of the extremity. The idea of exercising an extremity for detection of signs of arterial insufficiency is not new but a look at current text books on physical diagnosis and on cardiovascular diagnosis reveals that rarely do they discuss post-exercise changes. Some do note disappearance of pulses, whiteness of the foot, appearance of arterial murmurs after exercise in patients with arterial insufficiency of the leg but do not consider production of or significance of audible diastolic arterial murmurs after exercise.

Normally no murmur is audible over an artery if the stethoscope is applied lightly to avoid compression. Occasionally murmurs originating in the heart can be heard in peripheral arteries and it is necessary to recognize and exclude such murmurs. When a systolic murmur is heard over an artery it is caused by turbulent flow within the vessel and an abnormality of its lumen. If we exclude external compression such as occurs in hepatoma, or carcinoma of the head of the pancreas, then a systolic murmur must be due to irregularity of the intima due to arteriosclerosis.

An audible systolic murmur over an artery is not always indicative of clinically significant stenosis. But when a systolic murmur over a large artery to an extremity extends without interruption into diastole after exercise of that extremity it does indicate prominent arterial stenosis with inadequate collateral flow around the stenosis during the time the diastolic component of the murmur is audible. This phenomenon was well illustrated in Garrison's cases in which they had their greatest intensity in the area of arterial stenosis. In the patients in whom the stenosis is severe, then diastolic murmurs may even be heard during resting if the collateral circulation is impaired. Of course, one must be alert to exclude ductus arteriosus, arteriovenous fistula, venous hums as well as vascular tumors.

The dynamics of murmur production may be explained as follows: proximal to the stenosis, exercise raises the arterial pressure although there is little change in diastolic pressure, whereas distal to the obstruction the diastolic pressure falls during exercise because there is increased run off. This increase in pressure gradient across the stenotic artery during diastole produces a forward flow across a narrowed artery and a diastolic murmur as long as the pressure gradient persists, usually several minutes after exercise has been discontinued. The systolic component is made louder because of the larger pressure gradient across the stenosis during systole.

The absence of palpable extremity pulses indicates definite impairment of normal flow. What is not often appreciated is that patients with intermittent claudication in an arm or leg may have pedal or radial pulses at rest that will diminish or completely disappear after the involved extremity is exercised. Thus diminution of pulses after exercise is merely a reflection of the increased blood flow to the skeletal muscle in the presence of arterial disease and this prevents the delivery of an adequate increase in blood flow to the extremity.

The mere fact that the usual signs of arterial insufficiency in a lower extremity such as blanching of the skin of the foot upon elevation and the appearance of rubor after dependency, are not prominent does not rule out arterial insufficiency since there are patients with intermittent claudication that do not exhibit these changes, but exercise will produce them by causing a selective shunting of blood from the skin to the muscles. After several minutes of rest these signs will disappear.

In the arm significant stenosis of the subclavian artery is less common than it is in the iliofemoral arteries and typical claudication is unusual. But if a lesion in the artery is present then easy fatigability in the involved limb will become manifest and ischemic pain after deliberate exercise will appear together in some cases with signs of cerebral arterial insufficiency due to diversion of blood from the vertebral to axillary artery.[3] Careful observation here also will reveal alteration in pulses, skin color and murmurs over the subclavian artery characteristic of arterial insufficiency.

A final question is whether exercise is damaging to an impaired extremity when it is carried to the point of producing ischemia of the skin or foot. The answer is no, since ischemia so produced is only brief and in fact is itself a potent factor in promoting collateral circulation. Furthermore, the amount of exercise required to produce the changes described above is usually no more than the patient himself performs in the course of conventional daily activity.

Garrison's and other reports point up the importance of a meticulous physical examination of all patients suspected of having peripheral arterial insufficiency. The examination should include palpation of all pulses, auscultation of accessible arteries, notation of skin color before and especially after exercise of the extremity involved.

L.H.N.

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Cor Pulmonale In Recurrent Pulmonary Embolism

Recognition of the magnitude of the problem of pulmonary embolism has changed from 18 per cent of autopsies in 1918 to 66 per cent in 1965. This means that the frequency of finding emboli in the pulmonary arteries depends entirely on the thoroughness of the examination.[1] This has been assisted by such recently developed techniques and special procedures including scintiscanning pulmonary and bronchial arteriography, measurements of blood flow and ventilation with radioactive gases. The not so special procedures include a high index of suspicion, a careful history, which promotes a thoughtful review of the previous and present roentgenograms.

A question now in our minds is how many of the cases of pulmonary embolism have clinical significance, how many or how few of them could ever have been diagnoses during life and how many require treatment or were self limited and finally how should we separate one from the others. These and other questions are now in the process of being answered.

One point of great significance is that a great number and apparently the majority of embolic episodes occur without any infarct formation, probably no more than five per cent and not even when a main pulmonary artery trunk or small arteries are occluded. This means that if we rely on radiologic evidence of pulmonary shadows, or on physical and clinical signs of infarction we will recognize pulmonary embolism in no more than five per cent of cases.

It is in the patient with chronic recurrent embolization where the index of suspicion is usually low. Fleischner's[2] review presents illustrations for the insidious developing pulmonary hypertension in patients with old leg injuries and thrombophlebitis and post-puerperal cor-pulmonale. More common probably than these are patients without any antecedent suggestive history. Since pulmonary hypertension at rest does not occur until two-thirds or more of the vascular bed has been obliterated, radiologic signs are not evident until hypertension is moderate or severe. It is, therefore, the clinician who has the opportunity to suspect and to confirm the diagnosis of chronic recurrent emboli many years before the radiologic signs become evident.

The cardinal signs and symptoms of chronic embolization are exertional dyspnea, fatigue and chronic hyperventilation in the presence of a normal chest X-ray and normal mechanisms of breathing. We must be careful not to attribute the patient's dyspnea to a respiratory neurosis or hyperventilation syndrome. We must not label such patients as possible malingerers only to change our minds after radiologic evidence of pulmonary hypertension becomes unmistakable. Such signs are late in coming and may not show up until cor-pulmonale becomes obvious.

Cor-pulmonale stands out fairly well radiologically in embolic pulmonary hypertension. There are dilated hilar arteries, dilated pulmonary artery trunk evidence of right inflow stasis with widening of the superior vena cava and azygos vein and in rarer cases discernible dilatation of the right ventricle and atrium. Essentially we see a heart little or moderately dilated in its transverse diameter with marked dilatation of the pulmonary trunk and right ventricle in the lateral view.

The hilar arteries are dilated either by pulmonary hypertension or by embolic thrombotic masses lodged there. This makes the hilar shadows plump, sometimes tumor-like with a convex lateral contour and "amputated tail." The lung beyond the obstruction is under-perfused, the vascular arborization is diminished, often hardly visible, and the lung field in its entirety is over-lucent owing to reduced perfusion in the obstructed lung.

What is also important in Fleischner's review is that many cases of pulmonary artery hypertension which were formerly regarded as being caused by primary pathologic changes in the vessels, are now being recognized as secondary to repeated silent embolism. From the hemodynamic point of view we have in the last few years come to recognize that the most important cause of pulmonary hypertension is not organic vascular change but vascular spasm resulting from anoxia due to underventilation. It may be caused by emphysema and gross obesity neither of which is difficult to recognize. When underventilation is caused by chronic bronchitis without parenchymal disruption or of the "primary" variety, then differentiation from cor-pulmonale due to recurrent embolism may not be possible from the radiologic appearance alone.

Recurrent episodes of pulmonary embolism are not quite so "silent" if one learns to interpret pulmonary events accompanied by chest pain, dyspnea and hemoptysis. We must be alert to the significance of developing exertional dyspnea in the absence of congestive heart failure. We must give more attention to small pleural effusions and radiologically fleeting infarcts and not interpret them as pneumonia.

In medical practice, even if there is any doubt about the diagnosis, the patient is to be treated as if he had chronic thromboembolic disease, rather than primary pulmonary hypertension.

L.H.N.

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Mass Drug Catastrophes I. Alcohol

Alcohol in one form or another is used the world over for fun, ritual, social, and political celebrations. But is is used because it acts and in fact is a drug. The possibility of fatal poisoning by alcohol is not known by the laity today but we physicians know that death after drinking is not a rarity. In early times before the distillation process was discovered, acute fatal alcoholic poisoning must have been rare because the fermentation process stops at twelve to fourteen per cent concentration and it would have required enormous quantities of fermented liquor to cause death. Now it is different.

The physical effects of chronic alcoholism upon the peripheral and central nervous system, the liver, of concomitant reduction of food intake and vitamins are now recognized by all physicians although these medical facts only came to be accepted in the 20th century. Alcohol has probably caused more disease than any other drug in man's history. It is recognized to be a major cause of social disability. There are at least 2,500,000 socially useless alcoholics in this country and about as many more whose productivity is curtailed by alcohol. It accounts for countless broken homes, broken marriages, serious auto accidents and other tragedies and much of our crime. It is also pleasurable, habit forming and addictive and causes physical disease, psychosis and death. In small amounts it is a mild prompt sedative, and not as is so widely assumed a stimulant at all.

We know ethyl alcohol damages the nervous system and liver. What does it do to heart? Different clinical syndromes of heart failure associated with alcoholism have been described as have been the clinical features of alcoholic cardiomyopathy, which is thought to be due to injury to the myocardium as a result of excessive and habitual consumption of alcohol over many years. Such variables, however, such as the intake of food and alcohol are extremely difficult to control and the question of whether ethanol has an intrinsic action on the myocardium which is unassociated with any nutritional deficiency requires precise differentiation. This was the object of Maines and Aldinger's[1] experiment on rats.

Sixty rats were alcohol intoxicated for seven months while they ate a good caloric diet and maintained a good weight. Forty rats were controls and twelve were alcoholic receiving also food and vitamin supplement. The alcohol intoxicated animals were sedated, lethargic, but hair, color, texture, appearance of the mucus membrane of nose, mouth, eyes and gastric mucosa were normal. The myocardial contractility in the alcoholic group changed little in the first four months but then began to fall off. Similar cardiotoxic effects had already been demonstrated in rat atria, turtle heart and on in-vivo experiments on dogs by Loomis.

The cardiovascular changes observed during chronic oral administration, then, can be stated as progressive depression in myocardial contractility accompanied by a decrease in both aortic blood pressure, heart rate and a marked tendency toward the production of cardiac arrhythmias. This last is a well recognized sequel in many patients with coronary artery disease after a bout of alcoholism.

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Lilly

Since alcohol is a primary depressant of the central nervous system, myocardial depression may also be partially attributed to a direct reduction in central cardiac and vasomotor activity. It may very well be that depletion of norepinephrin at the betareceptor sites in the myocardium contribute to the cardiovascular depression observed by Maines in his alcoholic rats.

If alcohol damages the myocardium there should be present metabolic alterations and also histological changes in the myocardial cell. Ferrans et al[2] have shown accumulation of lipids in myocardial fibers as well as varying degrees of mitochondrial damage of their enzymes. He also showed in the myocardium of patients with alcoholic cardiomyopathy swelling and rupture of mitochondria, alterations of mitochondrial crystal formation of dense intra-mitochondrial inclusions, swelling of endoplasmic reticulum and liquid droplets in the myocardial cells. Obviously mitochondria, the energy machine of myocardial cells of patients poisoned by alcohol, are grossly damaged. This is sufficient to account for myocardial depression observed in animals on chronic alcohol consumption.

Damage to mitochondria alters the oxidative enzymes in the myocardium of alcoholic patients and leads to their release into the plasma. There then follows a process of widespread myocardial degeneration with the end result of cell death, healing by fibrosis and the characteristic electrocardiographic changes already described.[3]

In those clinical cases in which no overt evidence of malnutrition or vitamin deficiency was seen, it is not surprising that the production of alcoholic cardiomyopathy should have been attributed to excessive consumption of alcohol over a long period of time.[4] The pathologic effects of chronic ingestion of alcohol seen in rats by Maines and Aldinger support these clinical hypotheses and suggest that alcohol itself is directly instrumental in the production of heart disease. Apparently Montezuma's revenge on civilization has led to damage to five million individuals, some of whom also suffer myocardial injury, and it shows no signs of abating.[5]

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Metabolic Disorders In Human Atherosclerosis

With the control of acute disease in our grasp we are turning to prevention and treatment of the chronic illnesses. With regard to one disease, atherosclerosis, there is coming to be accepted the view that it is in large measure a metabolic disease. Genetic factors, genetic types of hyperlipidemia, disturbances of carbohydrate metabolism in relation to cardiovascular disease and early diabetic states are risk factors, are somehow determinants of arterial degeneration. This does not deny other known important influences, particularly smoking, hypertension, and hyperuricemia which of course is also a metabolic disorder.

If atherosclerosis is in large measure a metabolic disease the question is whether this is the only mechanism or whether it is but one of the pathways that cause the arterial lesion. Until recently large numbers of seemingly unconnected phenomena have been noted, but a coherent picture to explain the metabolic basis of arterial degeneration is only now beginning to emerge.

There now appears to be three metabolic patterns that are probably related to a predisposition towards atherosclerosis. One which has stood the test of time is the relationship between levels of serum cholesterol and atherosclerosis. In fact most of us now take this for granted and are beginning to study our patients for elevated serum cholesterol levels. We are searching for diets and now drugs that can help to reduce serum cholesterol and hopefully to prevent the development or progression of atherosclerosis.

A second metabolic abnormality presents as hypertriglyceridemia whose hallmark is a tendency towards elevation of the lipoproteins in the Sf 20-400 class. A third is the various stages of diabetes. Presumably this type must be considered as an independent metabolic error in its own right which is associated with the clinical complications of atherosclerosis.

We still have by no means established how much these patterns overlap, and to what extent they overlap. Neither have we clarified how environmental stresses such as diet unmask the underlying genetic predispositions. If these issues can be clarified it should become possible to devise rational preventive therapy in a given individual since the treatment of each of the different abnormalities is not likely to be the same.

At a national symposium under the auspices of the Heart Association of Southeastern Pennsylvania, these issues on the metabolic basis of human atherosclerosis were discussed in February and somehow the variety of existing developments which have occurred in the past few years suddenly fell into some sort of order. Major emphasis was given to the description and mechanism of interrelationship between carbohydrate and lipid metabolism and the role of insulin. Most of the evidence produced suggests that there is a relative deficiency of insulin in proportion to the blood glucose level at every stage of diabetes. Obesity was found to influence the serum insulin level and it was emphasized that this must be taken into account when we attempt to relate the insulin response to the blood glucose level. Hyperlipidemia of any kind was not considered to be an intrinsic feature of early diabetes.

It was pointed out that a genetic predisposition to diabetes is very common in the general population and it is likely that a genetic predisposition to carbohydrate induced hyperlipemia is also frequent. It would be expected therefore that these two metabolic errors, if they are different could coexist in the same person quite often and increase the risk of developing arterial disease. It was pointed out that thickening of the muscle capillary basement membrane is probably the early vascular manifestation of diabetes, regardless of whether there are subtle abnormalities in glucose metabolism at this stage.

Carbohydrate induced hyperglyceridemia can usually be identified by electrophoresis and there is fair evidence that hyperinsulinism is a feature of this metabolic disorder. Sucrose appears to induce this type of hyperglyceridemia more readily than complex carbohydrates. There was however no agreement as to whether carbohydrate intolerance in the absence of obesity is also an essential fact of this abnormality. Fat induced hyperglyceridemia was found to be rare and responded well to a very low fat diet and the results were not adversely affected if medium chain fatty acid supplements were added.

Important evidence was presented that Clofibrate (Astromid-S) not only lowers triglycerides and usually serum cholesterol but causes a net loss of cholesterol from the body. Whether this latter is good or bad remains to be determined.

The real question that pervaded the conference was whether hypercholesterolemia, diabetes and carbohydrate induced hypertriglyceridemia predispose to coronary heart disease. The evidence of the effect of elevated serum cholesterol levels was accepted by all. To what extent the other two metabolic errors associated with impaired glucose tolerance as measured by standard tests are easily risk factors was not clarified. There is evidence that hyperglycemia must be considered a likely risk factor towards the clinical manifestations of atherosclerosis.

It was apparent that glucose intolerance and hyperglyceridemia do not necessarily coexist. Nor was it established to what extent elevated serum triglyceride levels may be a risk factor in coronary artery disease in the same sense as serum cholesterol, smoking, hypertension and hyperuricemia.

All of this is very exciting and intensive efforts are bound to be made on the clinical, laboratory and epidemologic fronts to disentangle these complex and important interrelationships. In the meantime the practicing physician who wishes to make a determined effort to identify persons prone to coronary artery disease can no longer be content to measure only serum cholesterol. He must understand whether there is present carbohydrate intolerance, measure serum triglycerides in the experimental laboratory and they may even perform a muscle biopsy to learn whether basement membrane thickening exists. All of these characteristics have variable genetic as well as environmental components although their relative importance to the general population is not yet firmly established.

There is as yet no absolute proof to what extent these various metabolic derangements are associated with clinical disease, neither do we know whether their correction will prevent premature coronary or other arterial disease. Nevertheless we do believe in correcting metabolic derangements on general principle. Besides this self-evident truth, the clear recognition of several new hypotheses has opened the road to more intensive and better focused research. There is every reason to think that these efforts will be creative and yield clues to the prevention and control of atherosclerotic disease.

L.H.N.

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Factors In The Formation Of The White Thrombus

It is perhaps easiest to think of the formation of the white thrombus as an exaggeration of the reactions that occur in a transected vessel. Here we have two antagonistic forces at work, one the formation of a thrombus and second the antagonistic forces operating to prevent its development or to prevent its spread.

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plug that provides the initial defense against blood loss. In this phase, the blood coagulation mechanism is not primarily involved but rather an interaction between the vessel wall and circulating platelets. The smooth muscle cells investing the blood vessel contract. Nothing else happens unless there is also disruption of the endothelial cell lining in which case the lumen is exposed to a large layer of loosely packed collagen.[1-4]

When the platelets are exposed to collagen they undergo a remarkable transformation. They are attracted to and adhere to the collagen. They then swell, lose their architecture and release many of their intracellular constituents into the ambient blood. Serotonin is one which enhances vascular constriction. Adenosine diphosphate (A.D.P.) is another which has the property of causing rapid aggregation of platelets but not their destruction.[3] This makes it possible for platelet aggregation caused by A.D.P. to be reversed. It has also been repeatedly demonstrated that fibrinogen must be present for A.D.P. to aggregate platelets. It is of importance therapeutically that large doses of heparin or coumarins do not prevent platelet transformation on contact with collagen.

The second phase of hemostasis involves the conversion of prothrombin to thrombin which transforms fibrinogen into fibrin. Prothrombin may also be activated by tissue thromboplastin which is present in many blood vessel walls particularly that of lungs and brain. Thrombin also has a profound influence on platelets causing them to aggregate, swell and release their contents in a fashion similar to that which occurs when platelets are exposed to collagen.

The forces that lead to the formation of the hemostatic plug which occludes vessels must be balanced by limiting reactions, a balance between activation of the blood coagulation mechanism and those that limit the clotting process.[1] It is the limiting forces that consist of retardation of the formation of thrombin and its eventual disappearance and the dissolution of the formed clot. There is thus development of inhibitors against blood clotting factors, consumption or inactivation of some blood clotting factors during the process of coagulation and the activation of the fibrinolytic mechanism. Tissue activators of plasminogen are released which produce plasmin and the enzyme in turn attacks fibrin and some blood clotting factors. Apparently plasmin also attacks fibrinogen whose breakdown also releases inhibitors.

In addition to the three factors operating against in vivo blood coagulation there are two others of considerable importance. The growth of the hemostatic plug is diluted by rapid blood flow which sweeps away coagulation factors and mechanically opposes the unlimited growth of loose platelets aggregates. Another mechanism described by Deykin[1] is removal by the liver of activated forms of certain blood coagulation products. There are thus really five factors that oppose the unchecked accretion of the hemostatic plug: dilution by blood flow, hepatic clearance mechanism, appearance of specific inhibitors, activation of the blood fibrinolytic system and consumption of certain blood coagulation factors.

The white thrombus which forms in arteries consists primarily of a platelet fibrin mass much as that which occurs in a transected vessel. The initiating event is the interaction of circulating platelets with an abnormal vessel wall generated in most instances by the existence of an atherosclerotic placque but in others from other lesions that interrupt the normal endothelial barrier. Initially there is platelet interaction at the exposed surface of the arterial wall with progressive accretion of a fibrin platelet mass. In the large vessels the platelet mass is initially non-occlusive but grows continually as the blood stream brings to it a new supply of platelets.

Counterbalancing the accretion force is the disruptive force of the blood stream which sweeps away the most peripheral parts of the newly formed thrombus. Thus the white thrombus initially tends to be mural in configurations. As the mural thrombus continues to grow perhaps in association with extension of expansion of the underlying lesion the circulation in the immediate area slows. Finally as the circulation is completely occluded thrombus formation proceeds entirely through the red thrombus mechanism leading to the propagating red tail.

With these mechanisms of the formation of the white thrombus in mind, the question is how this knowledge influences our concept of anticoagulation therapy in arterial thrombosis. Since the initial stimulus for the formation of the white thrombus proceeds through mechanisms that do not directly involve the blood clotting mechanism we would actually not expect anticoagulants to be of much benefit. A sober view of the literature of the last twenty years would lead us to the conclusion that anticoagulation therapy has little if any benefit in the prophylaxis of the arterial lesion.

A final question of course is whether any therapy presently exists that would effectively block aggregation of platelets. That induced by A.D.P. could be blocked but the chemicals are too toxic to use. Linolenic acid has been put forth as a substance that reduces platelet adhesiveness.[5] It is a harmless food but needs further corroboration before it can be considered a truly useful prophylaxis against arterial thrombosis.

L.H.N.

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Disseminated Intravascular Coagulation

Besides the red thrombus and the white thrombus there is a third form of thrombus formation—the disseminated fibrin deposition in the microvasculature throughout the body particularly in the liver, kidney, spleen and brain. It is a reaction which generally requires in animals the injection of multiple doses of bacterial endotoxin. It can, however, be produced with a single injection of endotoxin if the reticuloendothelial systems is first blocked.

In man the diffuse deposition of fibrin throughout the body is seen in such clinical states as amniotic fluid embolism, incompatible blood transfusion reactions, malaria and the retained dead-fetus syndrome. Most of these syndromes are relatively infrequent. However, the widespread reintroduction of malaria into this country by returning soldiers from Viet Nam may significantly increase the incidence of disseminated intravascular coagulation caused by malaria.

It is obvious that the stimuli which activate the intrinsc mechanism to cause fibrin deposition in the microvasculature ought to be able to be derived from knowledge of the diseases in which disseminated thrombosis is found. It is probable that in these diseases substances may be liberated which like endotoxins in animals produce intravascular coagulation in man. In addition we need to know whether and in what way the liver is injured in the process, which finally leads to the crumbling of the whole hemostatic mechanism producing in the patient an apparently contradictory set of symptoms, on the one hand diffuse intravascular coagulation and on the other a widespread bleeding disorder. In animals one endotoxic injection is enough to cause intravascular clotting if the reticuloendothelial system is blocked.

Fibrin deposition will depend on which of the many complex factors that are involved in hemostasis are primarily altered. When one examines the fibrin deposits in the microvasculature in disseminated thrombosis one finds primarily red cells and fibrin—a meshwork in which some platelets are also trapped in a random fashion. This means fibrinogen is used up and platelets are used up. Furthermore, this type of thrombosis occurs in the micro vasculature where the blood flow is slowest, much as it is in the situations in the larger veins where the red thrombus forms. Here it will be remembered stasis combines with a state of hypercoagulability to facilitate the formation of the red thrombus.

It is postulated that in the above syndromes procoagulant materials are released into the blood stream and activate the blood clotting mechanism. The critical steps in this process are the conversion of prothrombin to thrombin and under the influence of thrombin the conversion of the soluble protein fibrinogen to an insoluble polymer fibrin. Prothrombin can also be converted to thrombin if thromboplastin, which is present in blood vessel walls, is liberated.

It is further postulated that the diffuse stimulation of the blood clotting system that follows the release of procoagulant materials in the blood stream produces an accumulation of fibrin within the blood that is at first removed by the hepatic reticulo-endothelial system. However, if fibrin continues to form and to be transported to the liver it ultimately blocks the hepatic sinusoids and disrupts the reticuloendothelial function. Blockade of the hepatic sinusoids leads to hepatic ischemia which may also block the ability of the liver to clear activated soluble blood coagulation factors. In any event as a result of progressive and unimpeded coagulation, all blood clotting factors including fibrinogen are used up, with the damaged liver being unable to replenish the fibrinogen supply.

Thrombin, however, continues to be produced and now it activates the fibrinolytic mechanism. It now attacks fibrin and degrades blood clotting factors. This is part of the fibrinolytic mechanism which is set into motion: first is the development of inhibitors against blood clotting factors such as V and VIII, prothrombin, platelets and fibrinogen. Plasmin is formed which attacks fibrin and blood clotting factors. The breakdown of fibrogen also releases inhibitors of clotting.

As a result of this complex interaction, fibrin deposition, failure of hepatic clearance, disappearance of fibrinogen and activation of the fibrinolytic mechanism, the whole hemostatic mechanism crumbles and the patient exhibits symptoms of diffuse intravascular coagulation as well as a widespread bleeding disorder. Obviously the proper clinical diagnosis rests on the recognition of a disease in which disseminated intravascular coagulation occurs. In such a state there should be found diminished clotting factors V and VIII, a marked reduction of fibrinogen as well as a low platelet level, because these are used up in the mesh of deposited fibrin.

If there is a hypercoagulable state as the basis of the process of disseminated intravascular coagulation, how does this knowledge influence our concepts of therapy in this grave condition. Since fibrin deposition is primarily due to a change in the blood clotting system itself one might expect a priori that anticoagulation by heparin would retard the rate of blood clotting and fibrin deposition and might be effective in the arrest of this serious disorder. This certainly has been shown to be true in carefully controlled clinical studies.

L.H.N.

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Subclavian Artery Obstruction

We should become more familiar with the vertebral axillary blood diversion syndrome to which our attention has been drawn only recently. The reason for this is that cerebrovascular insufficiency due to subclavian artery occlusion is more frequent than we have hitherto supposed. Furthermore it is very simply and easily diagnosed. Finally its diagnosis in selected cases can offer dramatic relief of symptoms if arterial reconstructive surgery is carried out successfully.

Contorini[1] in 1960 discovered the phenomenon of blood diversion from the vertebral to the axillary artery in the presence of subclavian artery obstruction. In the following year Reivich et al[2] reported two patients with subclavian obstruction in whom the blood from the brain was diverted through the vertebral into the axillary artery. It was they who showed the importance of the siphoning of blood from the cerebral circulation to the arm when there is proximal obstruction of the subclavian artery.

In an editorial appearing in the same issue of the New England[3] Journal of Medicine, the term "Subclavian Steal" was suggested to apply to this syndrome. It caught the fancy of the medical profession, but is not a physiologic concept of what actually takes place because it is the brain that is robbed of its blood supply to provide a collateral circulation for an ischemic arm.[4] A physiologic concept in which an area is robbed of its blood to supply another leads one to think of areas in the body other than the brain where this might occur. Is collateral circulation in the leg of this type? Is collateral circulation that develops in the heart of a type in which the right or left ventricle is deprived of blood to nourish another? How badly does the deprived area fare? These are all physiologic questions that arise from the concept of blood diversion that takes place during developing collateral circulation. When a concept is fruitful some of its consequences may indeed be rewarding.

Since 1961 many cases of subclavian obstruction with blood diversion to the arm from the vertebral artery have been described. In the literature there is documentation of 125 such patients since 1964 and several articles documenting symptomatic relief after successful arterial reconstructive surgery have since appeared. The symptoms are those of cerebral insufficiency. Transient blurring of vision, syncopal episodes, lateralizing motor or sensory signs, aphasia, and dysarthria, are not uncommon. The symptoms could be precipitated if the patient suddenly arose or turned his head to one side. Occasionally exercise of the arm can precipitate an attack and leave aching and weakness of the affected side. Some patients suffered from recent inability to concentrate, memory loss, and mental dulness. Such symptoms often attributed to "old age" were improved after surgical reconstruction.

The physical examination reveals the classic signs of inadequate blood flow to the arm. It may be cooler, blanch on elevation. There is weak or absent radial pulse on the affected side and a marked reduction of over 20 mm. of mercury pressure on the affected side. The auscultatory sounds are softer in intensity on this side. If there is incomplete occlusion of the subclavian artery, then a prominent systolic bruit can be heard beneath the middle of the clavicle. Once the occlusion becomes complete then the bruit disappears. Excellent visualization of the subclavian obstruction can be obtained by angiography and over half of the patients show retrograde vertebral flow. It is not however without its hazards since in one of three of Wheeler's patients[5] transtracheal arteriography resulted in thrombosis at the site of the catheter.

While angiography is responsible for our increased awareness of the frequency and importance of subclavian artery occlusion, it is the physical examination that can establish the diagnosis in most patients by a simple comparison of the blood pressure and pulse in both arms. If the occlusion is not complete then there is the added sign of a loud rough systolic murmur over the subclavian artery. However an absent subclavicular murmur may merely mean that the artery is totally occluded.

Obviously surgeons are reluctant to operate on a patient who does not have a pressure gradient in the arms or of course if the vertebral artery is closed or if there is a hemodynamically insufficient lesion. It is for these reasons Wheeler points out that we need good visualization by angiography which he performs by percutaneous transfemoral catheterization of the aortic arch. By this method and by pathological studies, it has been established that subclavian artery obstruction is characteristically short and segmental and therefore favorable for surgical reconstruction.

It is interesting that the first case of successful reconstruction of the subclavian artery with relief of neurologic symptoms was reported by Davis, Grove and Julian[6] over a decade ago. We may now expect many more such patients to be recognized and surgically relieved as we search all our patients suffering from cerebrovascular disease for this curable abnormality of the subclavian artery. Wheeler's collection of twenty two patients over a five year period in a small three hundred bed hospital indicates that there are many more patients waiting for recognition of this syndrome.

L.H.N.

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Platelets, Fatty Acids And Thrombosis

An elevated concentration of free fatty acids (FFA) has been found in certain pathologic and physiologic conditions associated with thromboembolic complications. Accordingly the question arises whether lipids have a potential to cause thrombosis directly. Hoak et al[1] in an earlier study found that injection of sodium stearate in animals produced thrombi which had the morphological features of natural thrombi rather than that of blood clots because electron microscopy revealed that platelet aggregates formed conspicious components of these thrombi.

In a more recent extension of the earlier observations, Hoak et al undertook a further study of other fatty acids as well as stearate upon platelet aggregation in vitro with the use of a turbidimetric method. In this connection it is well to remember that in arteries it is the white thrombus composed of platelets which forms the base for arterial occlusions by thrombosis.

Sodium stearate caused prompt aggregation in a suspension of washed platelets. This aggregation was partially inhibited by the addition of albumin although some aggregation still occurred. When stearate was added to citrated rich plasma it also caused prompt microscopic aggregation of platelets and it was not inhibited by heparin in concentrations as high as six units of heparin/ml. of plasma. The presence of calcium seems to be a necessary condition besides the stearate for the aggregation of platelets to take place, for if calcium is removed by EDTA, then no aggregation takes place. We must remember, however, that this type of observation does not rule out a direct effect of EDTA aside from its calcium binding.

Linolenic acid produced a prompt aggregation of platelets also when it was added to washed platelets. However, the story was different when linolenic acid was added to a platelet rich plasma solution, for now there was distinctly less platelet aggregation. It would be interesting to perform this experiment with normal platelet content of plasma. Then the differences between the fatty acids in their effect upon platelet adhesiveness might represent a closer approximation to the normal in vivo condition.

The real question is how does this aggregation occur and whether there is a mechanism which operates in-vivo to promote white thrombus formation in arteries. One could speculate that the free fatty acids cause a release of ADP from platelets. But this could hardly be so since platelet aggregation as a result of ADP is reversible and in the experiments by Hoak they were not. Then there is a possibility of release of serotonin and histamine. Further work along these lines is indicated.

Mahadevan[2] also found that long chain saturated fatty acids and oleic acid produced platelet aggregation in platelet suspensions, but linoleic and linolenic acids were ineffective. Ardlie et al[3] on the other hand found low concentrations of stearic acid ineffective in causing platelet aggregation unless there was also present in the medium epinephrin and ATP. Such variability in results with fatty acids on platelet aggregation probably reflects the different concentrations used in platelets and fatty acids as well as the influence of binding sites by plasma albumin. The last is very important since the unsaturated fatty acids are known to be bound more rapidly by albumin that are long chain saturated acids.

Then, of course, any discussion of platelet aggregation studies must take into account the limitations of turbidimetric methods. In general the turbidimetric method seems to be an easy and satisfactory procedure but it may overlook small aggregation which may be present and cause no change in optical density. In Hoak's studies not only the turbidimetric method was used but also phase contrast microscopy was employed before and after the addition of agents being tested for aggregating properties. Although by this method microscopic aggregation of platelets occurred with linolenic acid, in platelet rich plasma, in platelet normal plasma such an effect would be even less evident although this remains to be studied further.

The relevance of these results of in-vitro studies to clinical thrombosis obviously remains speculative, since the important question is whether plasma FFA which circulate bound to albumin ever produce aggregation and thrombosis in the body when platelets are in normal supply. The experimental evidence from experiments performed with fatty acids to date suggest that thrombosis will occur when the concentration in the blood rises above the saturation point of the two "tight" binding sites on the albumin molecule.

Goodman[4] found that if the plasma albumin concentration were 4 g/100 ml. then saturation of the tight binding sites would occur with a plasma FFA of 1150 to 1200 micro Eg./liter. We should remember that FFA of this level or greater have been found in a number of physiological and pathological conditions in which there is an increased frequency of thromboembolic complications such as diabetes, certain neoplastic diseases, hyperglycemia after myocardial infarction, and even in normal pregnancy and puerperium.

The hypothesis that fatty acids can produce hypercoagulability and thrombosis under more physiological conditions has been further supported by studies on rabbits who received subcutaneous injection of ACTH. In most such instances hypercoagulability and thrombosis occurred. These events were associated with high plasma FFA concentrations due to mobilization of endogenous lipids by the ACTH. The ACTH dose can be as low as 5 unit/kg. and still show increased thrombosis within one hour after the injection.

Several consequences of Hoak's and other studies should be born in mind. One is that heparin is inoperative against platelet aggregation produced by FFA. Another is that linolenic acid is the least damaging in the phenomenon of platelet adhesiveness promoted by fatty acids in the plasma. The obvious inference is that it is this unsaturated fatty acid that could be useful in avoiding the phenomenon of platelet adhesiveness in the formation of the white thrombus.[5]

L.H.N.

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Myocardial Degeneration Without Inflammation

McDermott et al[1] report on 28 patients who first appeared in the hospital with heart failure without any previous history of cardiac or pulmonary disease. None of the known causes of heart failure were present. However there were abnormal nutritional histories with heavy ingestion of alcoholic beverages primarily beer. Some however also took hard liquor in varying daily amounts from 60 ounces to as much as 300 per day! In May of 1966 a symposium in Quebec dealt with a similar type of heart failure also associated with beer ingestion which occurred in near epidemic form in that city.

The clinical findings were unmistakeable and impressive; dyspnea, weakness of short duration, massive cardiac enlargement without pulmonary edema, hypotension tachycardia, gallop rhythm, cyanosis and extreme right sided failure with an over-distended liver. There were a variety of electrocardiographic abnormalities particularly of P. and T., but conduction defects, ectopic beats, and arrhythmias were few.

The laboratory findings included lactic acidosis, and a remarkable elevation of serum enzyme levels. This combination gave indications of a grave prognosis and seems to be due to an associated hepatic necrosis found at autopsy.

The disease progressed rapidly since 11 of the 28 patients died in 72 hours. The 17 who survived had long periods of hospitalization and the subsequent prognosis is still uncertain. In some ways the disease represented a nutritional deficiency primarily of thiamine, a frequent finding in alcoholics and a recognized cause of beri-beri heart disease even without alcohol. However in the cases reported above it was not easy to diagnose thiamine deficiency as sole cause, because of uncertain therapeutic response to thiamine administration.

The histopathology of the heart was primarily that of cellular degeneration with vacuolization and edema. Neither inflammation or fibrosis was present. A significant difference between these patients and those with beri-beri heart disease[2] was the presence of centrilobular necrosis of the liver more severe than what one finds in congestive heart failure alone. In those who survived, liver biopsy showed nutritional fatty changes and nodular cirrhosis, obviously a healed state of hepatic necrosis. Clearly we have here a new entity, myocardial degeneration without inflammation and concomitant centrilobular necrosis of the liver.

There are numerous difficulties still present in determining the incidence or prevalence of this disease entity. It is reasonable to assume that for every severe case that appeared in the hospital, there must have been many more in the community not sick enough to require hospitalization. The fact that they all ingested large quantities of beer and some also hard liquor should direct ones attention to the relation of these cases to alcoholic cardiomyopathy.[3] The only point was that the disease was of brief duration, and high mortality. There was severe lactic acid accumulation, and unusual serum enzyme elevation, lack of neuropathy and no response to thiamin although thiamin deficiency was demonstrated in a few of the cases. This suggests that we are dealing here with a disease either produced or conditioned by nutritional deficiency. It must be remembered that thiamin requirements are increased when relatively large amounts of carbohydrate are ingested in the large amount of beer consumed.

The hepatic findings may of course have been due entirely to the massive heart failure but it is more likely that the patients had a concomitant form of liver disease perhaps viral in origin since the Quebec group found a high incidence of antibodies to influenza A in the serum of their patients.

The Quebec group also found additives in the brewing process of the beer that these patients consumed. One of the beers marketed in Nebraska also contained cobalt. The role of cobalt and other additives will now require assessment. One question is whether additives or an unknown factor in beer can act to inhibit thiamin and this idea certainly needs to be actively pursued.

Of course the myocardial degeneration could be a distinctly more complex disease than due to thiamin deficiency alone. There is the associated viral infection, and perhaps additional toxic factors all acting in concert to produce disease in a select population, especially in one in which excessive beer drinking has adversely affected the health of the victims.

At any event we must now be alert to a relatively new cardiac disease, myocardial degeneration without inflammation and be on the lookout for a combination of excessive beer drinking, viral hepatitis, toxic additives and thiamin deficiency, all interrelated in the production of this type of heart failure.

L.H.N.

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Coronary Vascular Disease And Hypertension

Introduction

Allan V. N. Goodyer, *Guest Editor*

About 50 per cent of all deaths in the United States in 1965 were caused by arteriosclerosis and hypertension, over 25 per cent being due to coronary vascular disease alone. Research endeavors have not yet uncovered the causes of these major diseases, but they have advanced our concepts of pathogenesis, and have provided new hopes for prevention and new methods for treatment.

In the present symposium, some of the recent advances in the fields of arteriosclerosis and hypertension are presented. The evidence implicating "risk factors" in the natural history of coronary vascular disease is discussed. Characteristics of pheochromocytomas, and methods for their detection and treatment in patients with hypertension are brought up to date. The causes and management of accellerated hypertension are reviewed, particularly in relation to the renin-angiotension-aldosterone system. Finally, the physiologic bases for new procedures for managing angina pectoris and for treating the shock and arrhythmias following myocardial infarction are presented, including particularly the use of electronic pacemaker, isuprel and xylocaine, and propranolol.

Although these articles present no dramatic solutions to the problems presented by patients with arteriosclerosis or the more common forms of hypertension, they provide some hope for reducing the ravages of these diseases in the near future, pending more final discoveries concerning their origins.

Coronary Shock

Richard E. Fearon, M.D.

Introduction

Presently shock remains defined in clinical terms as a syndrome of signs and symptoms reflecting a state of circulatory perfusion grossly inadequate for general tissue needs. The familiar signs include mental agitation or obtundation, cool, moist, pale skin, oliguria and usually a low indirect blood pressure measurement. More precise quantitation and definition of this disorder following myocardial infarction (coronary shock) have been delayed by the difficulties in performing physiologic studies on seriously ill patients. Since advent of coronary and shock care units, such studies, together with pertinent biochemical determinations, are now being reported.[1,2,3]

I plan to review present considerations concerning the pathophysiology and therapy of this disorder in light of these reports and animal experiments in our laboratory.

Pathophysiologic Considerations

All forms of shock result from inadequate cardiac output,[4] either secondary to a severely diminished ability of the heart to pump blood into the systemic circulation despite a normal or elevated filling pressure (cardiogenic shock), or as a consequence of inadequate venous return of blood to the heart. The reduced venous return may be secondary to hypovolemia (hemorrhagic, dysenteric, and traumatic shock) or sequestration of blood due to abnormal venodilatation (neurogenic shock) or abnormal venoconstriction (septic shock). Shock following myocardial infarction is primarily a form of cardiogenic shock in that the grossly inadequate cardiac output is mainly the result of a diminished pumping ability of the heart. The infarction not only decreases the mass of contracting myocardium, but may also diminish the effectiveness of the remaining normal myocardium by its paradoxic systolic pulsation.[5] An argument advanced to refute the concept of coronary shock as essentially a form of severe myocardial failure is based on the observation that the left-ventricular end diastolic pressure has not always been elevated in experimental coronary shock.[6] It is argued that the heart is therefore not failing. This argument fails to recognize that under conditions of low flow and pressure, the left-ventricular end diastolic pressure of the

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failing ventricle may be normal. An extreme example of this situation is the mean circulatory pressure of 7 mm. Hg. arrived at by the entire circulation following ventricular fibrillation in the normal dog (certainly an example of cardiogenic shock).[7]

Reflex mechanisms may have various roles in accentuating depression of myocardial function and cardiac output following myocardial infarction. First, pertinent experimental observations suggest the activation of reflexes which originate in the heart[8] and coronary arteries[9] during coronary occlusion and which prevent the expected compensatory peripheral vasoconstrictive responses to an acute drop in cardiac output. The possible importance of these reflexes on the arterial side of the circulation lies not in their role as major determinants of shock, as has been argued,[10] but as potentiators of hypotension which, in the presence of coronary artery disease, may further diminish coronary blood flow and thereby secondarily depress myocardial contractility. Second, Costantin has recorded decreased sympathetic activity in the inferior cardiac nerve of the cat during coronary occlusion.[8] While this effect was temporary, lasting only seconds, its presence suggests the possibility that if more prolonged cardiac sympathetic inactivity followed clinical coronary occlusion, cardiac contractility would be further reduced. Finally, the demonstration of baroreceptive areas in the left ventricle which are stimulated by left ventricular dilatation and which cause venodilatation[11] has led to the hypothesis that such a reflex may be operative following myocardial infarction. To the extent that venous return to the heart is reduced by venodilatation, the cardiac output would be lowered for a given level of myocardial contractility in accordance with the Frank-Starling mechanism. There has as yet been no experimental demonstration of this reflex following myocardial infarction.

The role of the cardiac output in influencing the clinical picture of shock has been questioned. While in the vast majority of instances in which the cardiac output has been measured in patients in shock following myocardial infarction it has been severely reduced,[6] there have been occasional instances wherein the reduced output has been no lower than that observed in some cardiac patients not in shock. It would seem more appropriate to consider that it is the degree of imbalance of blood flow to tissue need which determines the clinical syndrome. Accordingly, care has been taken to define shock in terms of "inadequate" cardiac output rather than degree of reduction. The results of studies of arterial blood lactate and pyruvate concentrations in patients in shock support this concept.[2,3] During hypoxia, aerobic oxidation of pyruvate in the Krebs cycle is limited, with a consequent increased anaerobic conversion of pyruvate to lactic acid. Calculation of the degree to which this shift in metabolism occurs in the form of "excess lactate" then serves as an index of tissue hypoxia, or oxygen debt.[12] In two clinical studies,[2,3] excess lactate has shown a consistent inverse correlation with the survival rates of patients in shock. Further use of these biochemical determinations in conjunction with measurements of cardiac output in patients with coronary shock are needed. It may well be that the level of excess lactate is not only a better indicator of the adequacy of blood flow than measurement of blood flow per se, but also a more quantitative index of the degree of circulatory impairment than the clinical signs alone. In the absence of facilities to measure blood lactate and pyruvate concentrations, a reasonable estimate of the degree of lacticacidemia may perhaps be made from measurement of the arterial pH,[2] provided there is no hypercapnia.

To have stated that shock remains defined by the clinical signs is not to imply that a grossly inadequate cardiac output cannot exist in the absence of those signs which are also dependent for their expression upon the neurovascular responses to the reduced cardiac output. Because of the variability of vasoconstrictive responses, the degree of hypotension commonly fails to correlate with the severity of shock. It has probably been sufficiently emphasized that a low systolic blood pressure of 80 mm. hg. does not alone indicate shock; it is not so well recognized that normal pressures may be seen in association with obviously inadequate tissue perfusion. The overemphasis on hypotension as an essential component of shock is not newly recognized,[13] but is oft repeated. A normal blood pressure in the presence of coronary shock is noted especially in patients with a history of hypertension. Conversely, where cutaneous vasoconstriction has apparently failed, another sign of shock, the cool, moist skin, may not be seen and hypotension may be pronounced. This situation has been especially seen in patients with coincident diabetes, malignancy, alcoholism, cirrhosis, and cor pulmonale.[14]

A final consideration relating to the blood pressure in shock is the frequent discrepancy between the value determined indirectly by auscultation of the Korotkoff sounds and that determined directly through an intra-arterial needle. Under conditions of low flow with severe peripheral vasoconstriction, the Korotkoff sounds over the brachial artery are related more to the velocity of flow than the absolute pressure.[15] Thus, in one study, indirect blood pressure measurement proved unreliable in 33% of patients in shock with a high peripheral vascular resistance (greater than 1500 dyne-sec.-cm.$^{-5}$).[15] These patients may have normal intra-arterial pressures in the absence of any audible Korotkoff sounds.

Therapy Of Coronary Shock

Ideally, patients with myocardial infarction and shock should be cared for in a well-staffed intensive care unit equipped to monitor cardiac rhythm, to measure central venous and direct brachial artery pressures, and to record dye-dilution curves for calculation of cardiac output. Whether, with our present therapeutic armamentarium, knowledge of the status of these physiologic variables will allow therapy that can decrease the high mortality rate (60-80%) of patients with coronary shock is not known, but it is clear that these measurements allow a rational approach to therapy. The variable responses of the peripheral vasculature to shock alluded to above are of clinical significance. The studies of Shillingford and Thomas[1] have clearly shown the frequent independence of blood pressure and cardiac output following clinical myocardial infarction. In addition, it is possible that these physiologic measurements would allow recognition of the patient likely to develop an inadequate cardiac output before overt clinical signs of shock have appeared. Earlier recognition may be important insofar as most studies have suggested an increased survival rate when shock is treated early. The ways in which knowledge of the status of these measurements may direct therapy will become apparent below.

While instrumentation allows more precise evaluation of the hemodynamic status of the patient, general measures in the treatment of coronary shock are very important and must not be neglected. Relief of hypoxemia, acidosis, and electrolyte disturbances contributes significantly to stability of rhythm, cardiac contractility,[16] and reactivity of the heart and vessels to sympathomimetic amines. Oxygen by BLB (Boothby, Lovelace, Bulbulian) mask should be immediately administered and an intravenous route secured. There is a strong clinical impression that relief of pain with morphine may relieve the signs of diminished circulatory perfusion. On the other hand, morphine must be given with care as excessive doses may potentiate hypotension by causing venodilation.[17] Although it is controversial whether vasopressor agents have increased the survival rate in coronary shock,[18] it does seem clear that these drugs do prolong life when hypotension is severe. Accordingly, a vasopressor drug (aramine or levophed) should be administered if the associated signs of shock are present and hypotension is persistent and severe (systolic blood pressure of 70 mm. Hg. or less) in an attempt to increase it to 90-100 mm. Hg. The desirability for increasing a very low pressure arises out of consideration for maintenance of coronary blood flow, which in the ischemic heart is mainly pressure-dependent. Excessive elevation of the pressure adds an additional workload to the heart and outweighs the advantages of increased coronary perfusion. The preference for these two vasopressors with both inotropic and vasoconstrictive properties instead of pure vasoconstrictors, methoxamine (vasoxyl) or phenylephrine (neosynephrine), is based on the temporary augmentation of cardiac output achieved with the former and not the latter.[19]

Severe rhythm disturbances are life threatening, potentially reversible, and demand early treatment. More subtle arrhythmias may contribute significantly to an inadequate cardiac output following myocardial infarction. The therapy of any arrhythmia is largely dictated by the seriousness of the associated hemodynamic impairment; accordingly their treatment in shock is vigorous. For purposes of therapeutic approach, the arrhythmias due to myocardial infarction may be grouped into three categories: 1.) tachyarrhythmia, 2.) bradycardia, 3.) extrasystoles. The tachyarrhythmias, excluding sinus tachycardia, are most rapidly and safely treated with direct-current countershock, and subsequent administration of one of the cardiac depressant drugs (xylocaine, procaine amide, quinidine) in maintenance doses to prevent recurrence. A relative bradycardia (rate less than 80-90/min.) accompanying shock is not uncommon and when treated may result in a significant increase in cardiac output.[20] Sinus bradycardia may respond to atropine 0.5-2.0 mg. intravenously and maintenance intramuscular doses as needed.[20] Isoproterenol (isuprel) 1-2 microgm./min. intravenously is also effective in this situation, but may be hazardous if ventricular premature beats are present. The placing of a transvenous pacing catheter into the right atrium is more time consuming than the administration of drugs and its use in sinus bradycardia with shock can await observation of the response to pharmacologic therapy. In atrioventricular block with bradycardia, nodal bradycardia, and slow idioventricular rhythm accompanying shock, a transvenous pacing cathether should be immediately inserted into the right ventricle. Isuprel should be given until pacing is initiated. Occasionally right atrial pacing will be effective in nodal bradycardia and sinus arrest, thereby allowing a significant contribution of atrial contraction to ventricular filling, with a subsequent augmentation of cardiac output and blood pressure. In standstill, percutaneous puncture of the right or left ventricle and insertion of electrode wires for pacing should be attempted if external massage and intracardiac epinephrine or isoproterenol have been ineffective. Finally, treatment of extrasystoles should be initiated when they are frequent (greater than 5/min.) or, in the case of ventricular extrasystole, when they occur early in the cycle with interruption of the T wave[21] or when they are multiforme. In these situations, the threat of impending atrial or ventricular tachyarrhythmia is imminent. In addition, frequent extrasystoles themselves can significantly diminish cardiac output. We have favored the use of intravenous xylocaine in these situations, as described by Lown.[22]

Once attempts to support the blood pressure, stabilize the rhythm, correct acidosis, and achieve arterial saturation have been instituted, the status of the patient should be reassessed. In perhaps 15 to 20% of cases these measures suffice not only to alleviate hypotension but also to improve cardiac output such that the other signs of shock relent. If, however, signs of shock persist despite support of the blood pressure, it is likely that the cardiac output remains inadequate, the persistance of which, it is now recognized, will often lead to increasing acidosis and hypoxemia, with resultant vascular refractoriness to aramine and levophed causing progressive hypotension and death. In addition to measurements of cardiac output, sequential determinations of arterial pH, pO_2, and lactate-pyruvate levels may help define such patients. It might be expected that progressive excess lacticacidemia and continued very low cardiac output reflect a deteriorating situation requiring reversal. These measurements are not yet available from studies of patient material. Our studies in dogs with experimental coronary shock following repeated embolization of the coronary arteries with microspheres support this expectation. The nearly 100% mortality rate of patients with continued clinical signs of shock at this point of therapy is also in accord with this concept. Accordingly, in these cases a second phase of therapy, aimed at increasing the cardiac output, merits consideration. Four methods of achieving this have been proposed and all remain experimental.

1. In view of the oft-observed normal venous pressure in coronary shock (possible a consequence of some of the mechanisms described under "Pathophysiologic Considerations"), it has been again suggested that expansion of the vascular volume may so increase the filling pressure of the heart as to increase the cardiac output via the Frank-Starling mechanism.[23] In some reported instances of coronary shock this has proved useful, but it must be remembered that the level of the central venous pressure (or right atrial pressure) is not a reflection of the pressure in the less-distensible left atrium and that at higher vascular volumes, a given fluid load will disproportionately increase the left atrial pressure compared to the right atrial pressure.[24] The clinical significance of these hemodynamic relationships lies in the potential production of pulmonary edema by this approach to therapy. In an attempt to determine a relationship between the right atrial and left ventricular end diastolic pressures which would allow estimation of the latter from measurement of the former during coronary shock, we have made simultaneous measurements of these two variables during dextran infusion in dogs in coronary shock following diffuse coronary occlusion (fig. 1). It is clear that there is no consistent relationship. The variability is probably in large part due to variable right ventricular responses to increases in pulmonary artery pressure, depending on the adequacy of coronary flow to the right ventricle. It should also be noted that quite high left ventricular end diastolic pressures may be seen with normal right atrial pressures, and that when slight increases in the latter occur during dextran infusion, the left ventricular end diastolic pressure is approaching oncotic pressure.

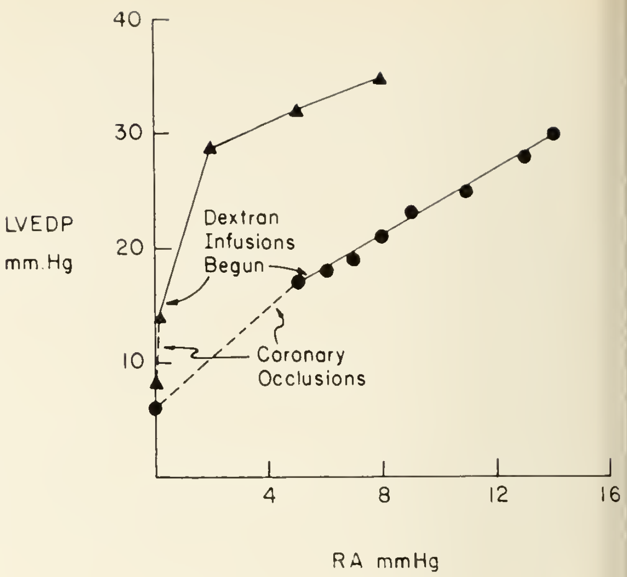

Figure 1

Two examples of the responses of left-ventricular end-diastolic pressure (LVEDP) and mean right atrial (R.A.) pressure to dextran infusions following experimental production of shock by coronary artery microsphere embolization. Measurement of the right atrial pressure does not allow prediction of the LVEDP. See text.

It must be pointed out that these pressure relationships are derived from an animal not previously in congestive heart failure before myocardial infarction. Clearly the right atrial pressure in patients with antecedent right heart failure is higher for a given left atrial pressure than in patients without such a history. In patients with antecedent right heart failure, the right atrial pressure may be elevated with fluid infusions to high levels before the onset of pulmonary congestion. This is a common observation following prosthetic valvular surgery.[25]

This method of increasing the cardiac output in coronary shock may be beneficial and reasonably safe if infusions are stopped as soon as the central venous pressure begins to rise, and particularly useful if there is hypovolemia which is often present after prolonged shock and prolonged levophed or aramine therapy. Whether the fluid should be low molecular weight dextran, regular dextran, or whole blood is an even less clear issue at present.

2. Lillehei and Bloch[26] have advocated the use of alpha adrenergic blocking agents, dibenzyline or regitine, plus volume expansion to increase venous return and tissue perfusion in cardiogenic shock. This approach has proved useful in the low-output syndrome following open heart surgery, but its use in clinical coronary shock, where maintenance of the blood pressure for perfusion of narrowed coronary vessels is of more concern, remains to be determined.

3. Several methods of assisted circulation have been described. The one with most theoretical potential for clinical use in the treatment of coronary shock is a reciprocating pump placed in series with the heart in such manner that during ventricular systole it removes blood via femoral cannulations, and during early diastole pumps blood back into the circulation.[27] The twofold aim is to reduce the systolic work of the heart, and hence its oxygen needs and to increase diastolic coronary flow, and hence oxygen availablity to the myocardium. It has been assumed that as a net result of these alterations, the anoxic heart would be in a more suitable condition to recover its ability to pump and thereby deliver an adequate output. Experimental and clinical reports have shown conflicting results.[27,28] While the oxygen needs of the heart seem to be better met with this arrangement, the general circulation shows inconsistent improvement with frequent failure of an increase in cardiac output. One reason for this failure may be the difficulty of timing the mechanical pump pulsation to coordinate with the variable timing of the spontaneous pulse wave at different levels of the aorta and major vessels.[29]

4. Finally, the approach to this problem which we are presently using depends on agents which increase myocardial contractility. Digitalis can significantly increase cardiac output in both experimental[30] and clinical coronary shock.[31] It has long been suspected, however, that digitalis increases the risk of arrhythmia in myocardial infarction. It has recently been demonstrated experimentally that digitalis does decrease the electrical stimulus required to induce an arrhythmia in a normal heart and increase the duration of diastole vulnerable to an electrically induced arrhythmia.[32] On the other hand, with lower doses than commonly used to treat congestive heart failure, it may be possible to avoid inducing arrhythmias in myocardial infarction.[33] We routinely give digoxin to patients in coronary shock, actually as part of the first phase of therapy.

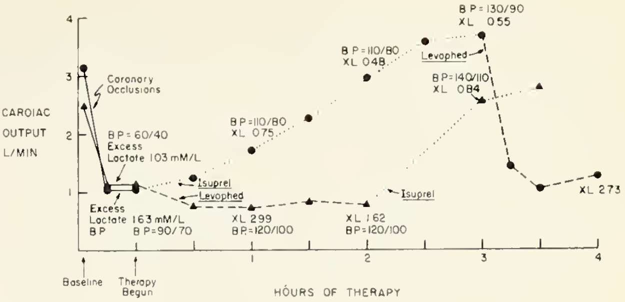

FIGURE II

Typical cardiac output responses in two dogs following production of coronary shock and during therapy with isuprel (.........) or levophed (------). The systemic excess lactate (XL) decreases during isuprel infusion but not during levophed infusion.

Isoproterenol, a beta-adrenergic agent, is a powerful inotropic stimulant with mild vasodilating effects. Unfortunately it potentiates arrhythmias, and for this reason must be given cautiously with constant monitoring of the rhythm. When using isuprel to treat coronary shock, we are presently administering a concomitant infusion of lidocaine (xylocaine) in an attempt to avert arrhythmias. The rationale for using an inotropic agent in a situation wherein the heart is damaged lies in the thought that by increasing the contractility of the uninvolved myocardium, an adequate cardiac output may be attained. This drug also acts as a coronary vasodilator[34] independent of its inotropic effects, (unlike norepinephrine) and in this way may improve coronary flow. We have been impressed with isolated successes clinically and with a definite superiority of isuprel over norepinephrine in the controlled experiments on dogs in coronary shock (fig. 2). In these experiments, the amount of xylocaine necessary to avoid arrhythmias has had little if any depressant effect on myocardial contractility. Careful volume expansion (made less likely to produce pulmonary edema by the inotropic effects of isuprel) concomitant with intravenous isuprel 1-4 microgm./min. and xylocaine 0.5-1.0 mg./min. constitutes our present preferred therapy of this second phase of coronary shock. Further clinical studies of the parameters mentioned and survival rates are necessary before this approach can be fully endorsed.

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The Adrenergic Nervous System In The Normal And Diseased Heart

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In recent years, the development of potent sympathetic blocking agents has made it feasible to evaluate the importance of the role played by adrenergic (sympathetic) innervation upon the cardiovascular system. Some of these agents are used extensively in the treatment of hypertension, while the newer beta-adrenergic blocking agents are still undergoing intensive evaluation of their usefulness in ischemic heart disease and a variety of other cardiovascular disorders. Not only are these agents therapeutic, but they are useful pharmacologic tools for study of the part played by the adrenergic system under normal and abnormal conditions.

Much background information concerning adrenergic function has been derived from animal studies. The development of an effective surgical technic for producing cardiac denervation (regional neuronal ablation)[1] has enabled the function of the canine heart to be studied at rest and under the stress of exercise following this procedure. These animals have been shown to be devoid of extrinsic neural control of the heart and after several weeks show a fixed heart rate (100-110 beats per minute) without sinus arrhythmia; and myocardial biopsies reveal extremely low cathecholamine levels.[2] Reinnervation of both the parasympathetic and sympathetic systems has been shown to occur in some of the animals by a year after the operative procedure.

The response of these cardiac denervated animals to exercise stress has been studied by Donald & Shepherd.[3,4] They show a delay in the development of the increased cardiac output response to exercise and the increased output which does occur is accounted for largely by an augmentation in stroke volume. Surprisingly, these animals did not show a deterioration in their capacity for sustained exercise as compared to normal animals. Thus, it appears that animals without adrenergic (and parasympathetic) control, and with presumably normal hearts otherwise, are able to perform adequately under certain types of stress, even though the mechanism of response is somewhat different. It should be pointed out that these animals were not exposed to a stress which would evoke a maximal cardiovascular response so that the cardiac reserve of the animals was not assessed. However, one would suspect that maximum cardiac performance would be depressed.

Since cardiac denervation by this technic essentially requires autotransplantation of the heart, these experiments provide important information about the manner in which a transplanted heart may function. If and when the immunologic and philosophic barriers to this procedure are overcome, it would appear that the transplanted heart could carry out reasonably adequate function.

Evaluation of the role of the adrenergic nerves on the human cardiac response has primarily depended upon the effect of blockade by pharmacologic agents. Guanethidine, which has been widely used for the treatment of hypertension, has a sympathetic blocking effect which appears to be independent[5] of its catecholamine-depleting effect. In studies designed to assess the effects of this agent on the human cardiovascular response to exercise,[6] six normal subjects were exposed to identical levels of supine leg exercise using a bicycle ergometer before and after 3 weeks of oral guanethidine administration. These investigations revealed that with identical levels of external work there was a reduction in mean heart rate (−9 per cent), cardiac index (−14 per cent), and left ventricular minute work (−21 per cent). Although these results indicated clear-cut impairment in association with sympathetic blockade, the degree of impairment was not great. The cause of the latter may be due to the moderate degree of exercise and the fact that it was performed in the supine position.

In the past few years a new type of agent has been found which blocks only the effects of beta-receptor stimulation. Ahlquist had clearly defined the scheme of two types of adrenergic receptors (alpha and beta) which were responsible for sympathetic stimulation.[7] These receptors were classified purely on a pharmacologic basis and the effects of a specific sympathomimetic drug depend on which of these receptors is stimulated (both may be stimulated by certain agents). The first type, the alpha receptor, generally produced a stimulating or excitatory effect while the second type, the beta receptor, generally produced an inhibitory effect on the effector cell. One of the major exceptions to this general rule occurred in the heart and it was found that cardiac excitatory effects were mediated via the beta receptors. The alpha receptors when

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stimulated caused constriction of blood vessels in the skin and in skeletal muscle.

Dichloroisoproterenol, the first agent of this type, was evaluated in 1958.[8] Because this drug was found to have some beta-adrenergic stimulatory effect also, it was not used for further clinical evaluation. The next agent, pronethalol, was found to be an effective beta adrenergic blocking agent and it was used in a number of clinical trials. It was subsequently shown to induce lymphosarcoma in the mouse and was removed from further clinical evaluation. Propranolol, the agent in current use, is about ten times more potent than pronethalol and has not been found to have a carcinogenic effect. Propranolol produces blockade of the beta receptors by competitive inhibition and thus the degree of blockade increases as the dosage of the drug is raised. This type of blockade is reversible and can be over-ridden by administration of isoproterenol, the classic beta-adrenergic stimulator. (Interestingly, although isoproterenol is not a naturally—occurring substance in the body, its cardiovascular effects most closely resemble those produced by exercise, i.e., increased cardiac rate and contractility and a decrease in net systemic vascular resistance).

With the development of propranolol, it was possible to evaluate the effects of blockade of the beta-adrenergic receptors while leaving the alpha-receptor mechanism intact. This allowed study of isolated blockade of cardiac stimulation while exposing a subject to various stresses. Normal individuals were evaluated while running at high speed in the erect position on a variable-incline treadmill.[9] Exercise levels producing exhaustion after several minutes were determined and after a suitable rest either a saline placebo or 0.15 mgm/kg of propranolol was given intravenously and the duration of exercise at the same intensity level was compared to the initial duration. The studies were repeated on successive days so that each of the nine subjects received both placebo and propranolol. Propranolol produced a mean reduction in the endurance time of 40 per cent, while the placebo had no effect on the endurance time. It was clear that following beta-adrenergic receptor blockade a normal subject was not capable of performing high intensity levels of erect exercise and exercise performance was substantially diminished.

Subsequently, some of these subjects underwent more elaborate investigations in which cardiac output (dye-dilution technic), arterial and central venous blood pressure, and oxygen consumption were measured during similar levels of erect treadmill exercise.[9] When compared to the control exercise condition, propranolol administration was associated with significant reductions in cardiac output (−22 per cent), heart rate (−19 per cent), mean arterial pressure (−15 per cent), and left ventricular minute work (−34 per cent) and a rise in central venous pressure (+2.8mm Hg). Beta-adrenergic blockade was associated with an impairment of the cardiovascular response to exercise and diminution in cardiac reserve and a reduction in the maximum oxygen uptake (−6 per cent). It is important to stress that although the cardiovascular response was impaired, an increase in cardiac output did occur and, as in the cardiac denervated dogs, it was brought about by other available compensatory mechanisms.

In addition to demonstrating that the adrenergic nervous system plays a significant part in the normal response to certain physiologic stresses, other studies have shown that this system plays a compensatory role in maintaining ventricular contractility when myocardial function is depressed by disease. Studies by Gaffney and Braunwald[10] have shown that the administration of guanethidine to patients with congestive heart failure will cause a worsening of the signs and symptoms of this condition in some of them. The results of these studies indicate that an important compensatory role is performed by the sympathetic nervous system and that worsening of myocardial function may develop when adrenergic blocking agents are administered to these patients. Other studies[11] have demonstrated that norepinephrine stores in cardiac muscle are strikingly reduced several weeks following the production of heart failure in experimental animals. Furthermore, myocardial biopsies taken from patients with advanced cardiac failure also demonstrate a reduction of norepinephrine.[12] It has been suggested that depletion of the myocardial neurotransmitter stores may be due to the chronic increase in sympathetic activity present in congestive heart failure. Finally, propranolol administration to normal subjects modifies the pattern of sodium excretion in the direction seen in patients with cardiac decompensation.[13]

With this background, an appraisal of the clinical effects of propranolol and its side effects can be better appreciated.

Clinical Use Of Beta-Adrenergic Blocking Agents

I. Angina pectoris. Both pronethalol and propranolol have been shown in controlled studies to be effective in reducing the frequency of angina pectoris. Early studies using propranolol for angina did not show a striking beneficial effect, but the initial drug dosage was low. A number of reports showing daily doses ranging from 90 mg up to 400 mg.[14-17] have clearly demonstrated its effectiveness. Although most patients do show a good therapeutic response, there is a small group of patients who do not show such an effect.

In our own group of patients the great majority

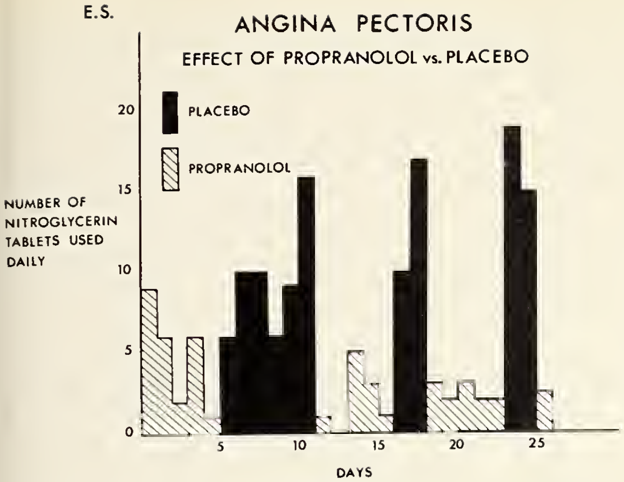

Figure I

The effect of propranolol on the nitroglycerin requirement in a patient with angina pectoris. The daily dose of propranolol was 40 mg per day from day 0 through 5 and 80 mg per day during the subsequent drug periods.

have shown clear-cut improvement while receiving propranolol* as compared to placebo. Some of these patients have shown complete absence of angina while most others show a definite and significant reduction in frequency (Fig. I). In patients who demonstrate no evidence of diminished cardiac reserve, the usual starting dose is 40 mg. given four times daily with an attempt to administer the drug at as close to 6 hour intervals as is practicable. As with other adrenergic blocking agents, propranolol may induce or aggravate congestive heart failure in patients with this propensity. In this type of patient, a smaller dose (10 mg four times daily) is given and this is gradually increased while observing the patient for the development or worsening of congestive symptoms and signs. If these occur, they can be managed, in most cases, by adding or modifying the digitalis and diuretic program. In some patients with obviously diminished cardiac reserve, digitalis and diuretics have been initiated before institution of propranolol therapy. Initial worsening of cardiac failure has been seen in a few patients, but it has not been necessary to discontinue the propranolol in any of these patients because of uncontrolled heart failure.**

What is the mechanism by which propranolol reduces the frequency of angina pectoris? A decrease in heart rate, cardiac output and left ventricular minute work occur with beta-adrenergic blockade. Studies reported by Wolfson et al[18] indicate that ventricular volume diminishes also in patients with ischemic heart disease at rest, but other investigations[19-20] indicate that ventricular dimensions are increased during exercise after propranolol administration. In Wolfson's study, some coronary vasoconstriction occurred with beta blockade in most resting patients although coronary vasodilatation did occur in one patient when propranolol was administered shortly after an anginal episode. In most studies, a decrease in cardiac work and in myocardial oxygen consumption occurs following propranolol administration and although there are a number of opposing factors involved, it appears that the diminished myocardial oxygen requirement is the major factor responsible for the decrease in angina pectoris.

Hamer and Sowton[21] have shown that exercise tolerance in patients with angina can be improved following intravenous propranolol. Of thirteen patients whose exercise was limited by anginal pain, five of these developed no pain and the remaining eight patients were able to increase the total amount of exercise by 60 per cent after beta-blockade. Slowing of the heart did not appear to be a critical factor in the production of angina since pain usually developed at a slower rate after propranolol. The combination of a beta-blocking agent and nitroglycerin given before exercise appears to produce a synergistic effect and results in a marked augmentation of exercise capacity.[22]

Does there appear to be a paradox here? On the one hand, it has been shown that propranolol decreases exercise tolerance in normal individuals and may induce congestive heart failure in patients with diminished cardiac reserve while on the other hand, there appears to be an increase in exercise tolerance in patients with angina. There is no real paradox since we are concerned with two different aspects of cardiac function. In the normal individual or the patient with poor cardiac reserve without angina a decrease in exercise tolerance results from a diminution in cardiac output or a rise in ventricular filling pressure resulting in fatigue or dyspnea. In contrast, the anginal patient is generally limited by the typical chest pain resulting from myocardial ischemia and this end point is usually reached before any limitation imposed by diminished myocardial reserve occurs. Thus it would seem likely that a patient with angina who is receiving propranolol would have a diminished cardiac reserve as compared to his non-propranolol state, but that in most patients this diminished reserve is not apparent because the limiting factor is still angina even though a greater degree of exercise may be required to induce the angina. In those anginal patients in whom there is very little margin between the angina threshold and the threshold imposed by a diminished functional reserve, there may be those who become limited by dyspnea or fatigue rather than angina, following beta blockade, but in our experience, this is quite uncommon.

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* Supplied as Inderal by Dr. A. Sahagian-Edwards of Ayerst Laboratories.

** These results will be reported in detail subsequently.

Thus, it appears that the beneficial effect of propranolol is due to diminished cardiac work and a reduction in the myocardial oxygen requirement. This would seem to be only a palliative means of therapy, however this benefit is readily welcomed by the patient. Our own experience was initially limited to patients with severe and intractable angina, but recently we have tended to use the drug in patients with less severe ischemic disease. Aside from the production of congestive heart failure which should be watched for, troublesome side effects from the drug are few and have been detailed elsewhere.[23]

II. Acute Myocardial Infarction

Snow[24,25] reported his initial results on the use of propranolol in patients with acute myocardial infarction. Alternate patients admitted with a history of myocardial infarction were given 30-60 mg of propranolol daily. The mortality rate in those who received propranolol was 13 per cent (7/52) while the mortality was 29 per cent (16/55) in those who did not receive the drug. There appeared to be fewer deaths from cardiac arrest and shock in the propranolol treated group and there did not appear to be an increased incidence of heart failure in this group. Snow readily admitted that there may have been some deficiencies in the design of his study and that, although the results were encouraging, the numbers were not large enough to permit a final assessment of the effect of propranolol in this condition.

Subsequently Balcon et al[26] studied 114 patients who were randomly given the drug or a placebo on a double blind basis. Only patients with heart block or coma were excluded from the study. Fifty patients had continuous electrocardiographic monitoring. The mortality rate in the propranolol group was 23.2 per cent (13/56) and was 24.1 per cent (14/58) in the placebo group. There was a higher incidence of sinus bradycardia in the propranolol group, but there was no apparent difference in other arrhythmias between the two groups. These workers concluded that there was no indication for the routine use of propranolol in acute myocardial infarction.

Clausen[27] evaluated 110 patients with acute myocardial infarction excluding only those patients with a history of asthma. Patients were randomly assigned on a double blind basis and continuous electrocardiographic monitoring was not carried out. There was no apparent difference in the incidence of arrhythmias in each group and the mortality rate in the propranolol (40 mg daily) group was 30 per cent while that of the placebo group was 33 per cent. Although the difference was not statistically significant, the mortality rate among propranolol treated patients with clinically moderate infarctions was lower than the corresponding controls while in patients with severe myocardial infarctions the mortality was higher in the propranolol group.

In a multi-center study,[28] 195 patients were randomly assigned to propranolol (80 mg daily) on a double blind basis without cardiac monitoring. Patients with asthma, a heart rate under 60 per minute, or a systolic blood pressure under 80 mm Hg were omitted so that many seriously ill patients were excluded. The mortality rate in the propranolol group was 15 per cent (15/100) while that of the placebo group was 12.6 per cent (12/95) and cardiac failure and hypotension occurred more than twice as frequently in the propranolol-treated patients.

Since 1966,[29] we have been conducting an evaluation of propranolol in acute myocardial infarction in the Coronary Care Unit of the Yale-New Haven Hospital. On admission to the Unit, each patient is evaluated and assigned a prognostic index figure based upon certain historical features and his physical condition. Patients with overt congestive heart failure, shock, heart block, asthma (including a history),[30] or reserpine therapy are immediately excluded from the study, but their course is followed and analyzed. If patient and physician consent is obtained, the eligible patients are randomly assigned to propranolol (20 mg. q6h) or placebo on a double blind basis. Eligible patients from whom consent is not obtained are also followed and analyzed. Continuous electrocardiographic monitoring is carried out for 72-120 hours. The total number of patients in the groups is still too small to demonstrate meaningful results, but the mortality rate in the propranolol group is 6.3 per cent (1/16) while in the placebo group it is 25 per cent (4/16). These two groups are reasonably comparable in the severity of illness. In the eligible group from whom consent was not obtained. the mortality rate was only 7.1 per cent (2/28), but this group was clearly not as severe as the two preceding groups. The most seriously ill group consisted of those patients excluded from the study and the mortality rate was 37 per cent (17/46). There has been no obvious difference in the frequency of cardiac arrhythmias between the propranolol and placebo groups. This study is being continued and it is hoped that some definitive answer will be forthcoming.

At the present time, there are conflicting data concerning the effectiveness of propranolol in patients with acute myocardial infarction. A number of variables are involved and the most important probably are severity of the clinical condition and the dosage of the agent. It is hoped that this situation may become clearer with further study.

Beta-adrenergic receptor blocking agents have been found to be useful in the treatment of various cardiac arrhythmias, especially those induced by digitalis intoxication. A full review of the beta-adrenergic blocking agents by Epstein and Braunwald[31] has recently appeared and this review should be consulted for information concerning the use of the agents in other conditions.

Summary

The importance of the role played by the adrenergic nervous system in the mediation of normal cardiovascular responses in animals and in man, has been discussed. The development of the beta-adrenergic receptor blocking agent, propranolol, has furnished a new pharmacologic tool for evaluating the effect of sympathetic stimulation on the normal and diseased heart. This agent has been shown to be effective in the treatment of angina pectoris while its usefulness in the management of acute myocardial infarction is still under evaluation. It is expected that this drug will be a useful addition to the armamentarium of the physician managing cardiovascular disorders, but as is the case with most potent drugs, care must be used in the proper selection of patients and in the observation for side effects.

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Pheochromocytoma: Diagnosis And Management

Robert J. Levine, M.D.

Pheochromocytomas are catecholamine-producing tumors that arise from chromaffin cells of either the adrenal medulla or the sympathetic nervous system. The importance of these tumors to the physician is disproportionate to their relative rarity. Patients harboring pheochromocytomas may present with any of a variety of spectacular clinical syndromes. The clinical manifestations may mimic so faithfully those of some other disease such as thyrotoxicosis, cardiomyopathy or emotional disturbance that the physician may be distracted for months, years or even forever from pursuing the correct diagnosis. Untreated pheochromocytoma usually causes the death of the patient; incorrect treatment may either hasten the lethal termination or cause permanent disability. On the other hand, the prompt implementation of correct diagnostic and therapeutic procedures usually results in complete cure of the disease.

In the past 15 years, specific chemical assays for catecholamines and their metabolites have been developed and, more recently, these tests have been made available in most good clinical chemistry laboratories. Our ability to manage these patients has also improved substantially in the past few years. An increasing number of patients with pheochromocytomas have had diagnoses made early enough to derive the fullest possible benefit from this improving therapy. In 1966, 6 patients with pheochromocytoma were treated on the medical and surgical services of the Yale-New Haven Medical Center (YNHMC) and the West Haven Veterans Administration Hospital (WHVAH). Unfortunately, in the same year, examples of patients in whom the diagnosis was made only terminally or at autopsy continued to appear in the literature (1, 2).

This article reviews the current concepts of the diagnosis of pheochromocytoma. Some recent developments in the management of patients with this tumor are discussed. References to some recent review articles are provided for those who may wish to read more detailed accounts of some aspects of this problem.

Clinical Presentation

The question is often asked: in a population of hypertensive patients, how does one select those on whom diagnostic tests for pheochromocytoma should be done? The answer is based upon the often repeated observation that many of these patients present no historical features or physical findings that distinguish them from patients with essential hypertension. The blood pressure elevations may be either sustained or paroxysmal; the hypertensive diathesis may be severe (malignant) at onset or may persist for many years as a benign, assymptomatic, low-grade elevation of blood pressure; responses to non-specific maneuvers such as rest and sedation or cold pressor tests are of no value in distinguishing between essential hypertension and pheochromocytoma. All patients with hypertension in whom the cause is not known should have at least one screening test for pheochromocytoma. The test should be a chemical test and it should be done under conditions that best assure the validity of the result.

The patient may present some clinical findings or associations that are particularly suggestive of pheochromocytoma (Table I). In such patients, one may wish to pursue the possibility of pheochromo-

TABLE I

FINDINGS SUGGESTIVE OF PHEOCHROMOCYTOMA

Clinical manifestations
- Paroxysmal attacks*
- Signs of excessive adrenergic stimulation
- Signs of hypermetabolism
- Orthostatic hypotension
- Anxiety—hyperexcitability

Laboratory findings
- Hyperglycemia
- High hematocrit

Associated conditions
- Neurofibromatosis (Von Recklinghausen's disease)
- Retinal angiomatosis (Von Hippel's disease)
- Multiple endocrine adenoma
- Medullary thyroid carcinoma

Family history of pheochromocytoma or of any of the associated conditions listed above.

* See text for discussion of paroxysmal attacks.

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TABLE II

METABOLISM OF NOREPINEPHRINE

ENZYME	SUBSTRATE	PRODUCT
Phenylethanolamine N-methyl transferase	Norepinephrine	Epinephrine
Catechol o-methyl transferase	Norepinephrine Epinephrine 3,4-dihydroxymandelic acid (DOMA)	Normetanephrine (NMN) Metanephrine (MN) Vanilmandelic acid (VMA)
Monoamine oxidase	Norepinephrine Epinephrine NMN and MN	DOMA DOMA VMA

Note that the catecholamines, norepinephrine and epinephrine may be either methylated to form NMN and MN, respectively, or oxidized to form DOMA. Those that are first methylated may then be oxidized and those that are first oxidized may then be methylated; either sequence results in the same end metabolite, VMA.

cytoma further even if the first chemical assay yields a negative result.

Paroxysmal attacks are, of course, the classic manifestation of pheochromocytoma. Most commonly the symptoms are obvious expressions of excessive effects of epinephrine or norepinephrine. Some patients have extreme elevations in blood pressure associated with headache, angina pectoris and/or blanching of the face and extremities; this reflects primarily α-receptor stimulation. In other patients, β-receptor effects seem to dominate; there may be sweating, facial flushing, rapid palpitations, fever and, occasionally, hypotension. In many patients these patterns may be mixed. Anxiety is likely to be associated with most attacks; the symptoms often are improperly attributed to anxiety.

A significant number of patients report episodes of bizarre complaints, the pathogenesis of which seems obscure.[1,3,4] For example, one man treated recently at YNHMC had complained for four years of nervousness and for two years of episodes of sudden tingling or itching in his scalp sometimes followed by a slow pounding of his heart. During one such attack his physician found that his systolic blood pressure was greater than 300 mm Hg. Subsequent to this observation, appropriate studies were undertaken that resulted in the diagnosis and successful surgical removal of a pheochromocytoma. We have come to regard almost any form of peculiar paroxysmal event in a hypertensive patient as sufficient provocation to pursue vigorously the diagnosis of pheochromocytoma.

Certain drug reactions also may be highly suggestive of pheochromocytoma. These patients may respond with increased rather than decreased blood pressure to antihypertensive agents that act by catecholamine release; e.g., guanethidine, reserpine and methyldopa.[5] This is particularly apt to occur when these drugs are given parenterally. Patients given insulin to combat hyperglycemia due to pheochromocytoma may experience severe catecholamine release phenomena. One patient at YNHMC recently underwent intravenous pyelography in the course of a routine hypertensive examination. He developed what seemed to be a mild allergic reaction followed by a very severe hypertensive crisis. Subsequently a large pheochromocytoma was discovered and removed. It appears that this patient may have experienced a rather novel equivalent of a histamine test associated with the allergic release of histamine.

Chemical Tests

The definitive diagnosis of pheochromocytoma almost always is established by assay of the catecholamines (epinephrine and norepinephrine) or their metabolites (VMA or metanephrines) in urine. In order to use these tests effectively, the physician should understand some basic aspects of catecholamine metabolism[6,7] (Table II).

The assays that are made available by clinical chemistry laboratories are VMA, total metanephrines (NMN plus MN) and free catecholamines. If done properly, all of these assays offer a high degree of both specificity and sensitivity in the diagnosis of pheochromocytoma.[4] Most commonly available in routine diagnostic laboratories is the VMA assay. It is technically easier to perform than the assay for catecholamines. Specific chemical assays for VMA are greatly preferred to the non-specific screening tests which often give false-positive results. Metanephrine assays are equal in simplicity and reliability to VMA assays; they are less widely offered by clinical chemistry laboratories owing to the fact that they were introduced later than the assays for VMA.

Catecholamine assays, though more expensive and difficult, offer one important advantage over assays for metabolites. It is possible to assay selectively for epinephrine and norepinephrine. Tumors associated with increased urinary excretion of epinephrine are virtually always found either in the adrenal medulla or in the organ of Zuckerkandl. It should be noted, however, that the obverse is not true. The finding of normal epinephrine excretion in a patient with pheochromocytoma and high urinary levels of norepinephrine is of no value in localizing the tumor.

It is essential to observe certain precautions in order to assure the validity of these tests. Preferably, these tests should be done on patients who are taking no drugs. Pressor amines found in many nasal decongestant, antiallergy and antiasthmatic preparations may cause false positive results in all of these tests. Methyldopa will increase catecholamine levels in urine; it is metabolized to an analog of norepinephrine. Monoamine oxidase inhibitors will increase metanephrines and decrease VMA. The physician should contact the laboratory before the test is ordered to find out what test they do and what additional precautions they recommend.

In some patients, long assymptomatic intervals may be associated with normal levels of catecholamines in the urine. The chances of obtaining a positive result are enhanced if urine is collected during a symptomatic period.

Pharmacologic Tests

Before reliable chemical assays became generally available physicians became quite dependent on pharmacologic tests for aid in the diagnosis of pheochromocytoma. These tests are dangerous; at this time, their use is recommended only in exceptional circumstances. Among the drastic results precipitated by positive tests are shock, cerebral hemorrhage and myocardial or cerebral infarction.

Intravenous administration of phentolamine (Regitine) to a patient with high blood pressure due to a pheochromocytoma will usually result in a prompt decrease in blood pressure.[8] This test may be of value in dealing with a patient who presents a life-threatening hypertensive crisis; e.g., encephalopathy or pulmonary edema. A positive test provides not only a diagnosis but also a means for treatment. Although the usual dose recommended is 5 mg., it is safer to try a smaller dose of 0.5 mg first.

The histamine provocative test may be of value in the patient with paroxysmal hypertension who, during a long period of observation, fails to have an attack and in whom urinary excretion of catecholamines or metabolites remains normal. Intravenous administration of histamine phosphate, 0.01 to 0.05 mg, will usually precipitate an attack.[8] The specificity of this test is enhanced if urine is collected for catecholamine assay for 2 hours before (control specimen) and for 2 hours after the test.

During the performance of either of these tests appropriate agents to combat excessive reactions should be kept readily available: norepinephrine for the phentolamine test and phentolamine for the histamine test.

The tyramine provocative test was introduced by Engelman and Sjoerdsma in 1964.[9] It seemed to offer an important advantage over the histamine test in that it was much safer. With small doses of tyramine a small but diagnostic elevation in blood pressure was obtained in their patients with pheochromocytoma. Also, the unpleasant flushing and headache associated even with negative histamine tests was not observed. Subsequently, Sheps and Maher reported that, in their series of patients with pheochromocytoma, the tyramine test lacked the sensitivity required for a reliable screening test.[10] The eventual status of this test remains to be determined with continued testing.

Localization Of The Tumor

Approximately 80 percent of all pheochromocytomas are found in the adrenal gland. The possible sites of extra-adrenal pheochromocytomas may be predicted on the basis of a knowledge of the distribution of chromaffin cells in the body.[3] These tumors have been found in association with sympathetic nerves in the neck, thorax, abdomen and pelvis. Extra-adrenal and multiple tumors are more likely to occur in children than in adults.

Important clues as to location of tumors may be obtained from the patient's history and physical examination. The attacks may be associated with some particular position or activity; e.g., a tumor of the bladder may cause symptoms in association with micturition. A mass may be felt in the neck or abdomen, pressure on which reproduces an attack.

Radiographic techniques are required to locate the tumor in most cases. Most of these tumors will be found by either intravenous pyelography with laminography of the renal and suprarenal areas or routine chest films.[4] Occasionally, more specialized techniques are required.[11] Retroperitoneal pneumography will provide satisfactory definition of most retroperitoneal structures and may be used in conjunction with dye-contrast procedures.[11,12] A method combining the safety of carbon dioxide with the convenience of air proposed by Lowman[13] is used at YNHMC. Arteriography may be useful in locating the tumor and in identifying its blood supply.[14] Injection of contrast dye into the artery supplying the tumor commonly precipitates a hypertensive response. This response can be useful diagnostically; it can also be dangerous. It is essential to be prepared to treat catecholamine release phenomena promptly during dye or gas contrast roentgenographic procedures in patients with pheochromocytoma.

Some tumors resist all efforts, including surgical, at localization. In these patients blood may be sampled by catheter from various sites in the inferior and superior vena cavae.[15] At the point of entry into the vena cava of the vein draining the tumor there may be an increase in plasma catecholamine levels.

Treatment

In most patients with pheochromocytoma surgical removal of the tumor results in complete and permanent cure of the disease. The special surgical and anesthetic problems presented by this disease are discussed in detail in a recent review[4] and are beyond the scope of this article. There are some relatively recent pharmacologic developments in the management of this disease that deserve comment here. These are of particular value in preparing patients for surgery and in the treatment of patients in whom surgery is not feasible either because of disseminated malignant pheochromocytoma or some other serious complication; e.g., myocardial infarction.

Drugs that block the effects of circulating catecholamines on adrenergic α-receptors have been known for a long time to be effective in the acute therapy of hypertension due to pheochromocytoma. Recently it has been demonstrated that oral administration of one such drug, phenoxybenzamine (Dibenzyline), may afford satisfactory control of hypertension for years.[4,16] Propanolol (Inderal) is an adrenergic β-receptor blocking agent that is now available only for investigational use.[17] This drug has been found effective in controlling tachycardia, arrhythmia and some other manifestations of excessive β-receptor activity in patients with pheochromocytoma. Another drug that now has an experimental status that shows promise in the treatment of this disease is α-methyl-para-tyrosine. This drug acts by inhibiting tyrosine-hydroxylase, the rate-limiting enzyme in the biosynthesis of catecholamines; its efficacy in patients with pheochromocytoma has been demonstrated.[18]

Summary

This article reviews the current concepts of diagnosis of pheochromocytoma. Some clinical manifestations and associations that are particularly suggestive of pheochromocytoma are outlined. It is emphasized that in most cases assay of catecholamines or their metabolites in urine is sufficient to establish the diagnosis. Pharmacologic tests are dangerous and their use is indicated infrequently. Methods available to localize tumors including specialized roentgenographic and chemical techniques are discussed. Finally, there are comments on some new pharmacologic approaches to management of patients with pheochromocytoma.

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Accelerated Hypertension–Mechanism And Treatment

Patrick J. Mulrow, M.D.

Clinical Description

Accelerated or malignant hypertension follows a rapidly progressive downhill course ending in death if untreated. It is a disease of young adults, with a peak incidence between the ages of 35 and 50. The diastolic blood pressure is persistently above 130 mm Hg. Hemorrhages, fluffy, white exudates and/or papilledema are seen in the eyegrounds, and renal damage evidenced by proteinuria, frequently hematuria and eventually nitrogen retention, is present. The early symptoms may be persistent headache, nocturia, increased nervousness, insomnia, weakness or blurred vision. The onset is often abrupt. Occasionally there are no symptoms until uremia is established. Accelerated hypertension is an uncommon development of essential hypertension, the reported frequency varying from 0.1 to 5 per cent. The 0.1 per cent figure is probably the more accurate estimation. Males, especially negro males, are more prone to develop it.[1,2]

Accelerated hypertension is a frequent occurrence in the uremic phase of chronic renal disease, especially chronic glomerulonephritis. Occasionally it develops in patients with pheochromocytoma but it rarely develops in patients with primary aldosteronism, Cushing's syndrome, or in patients without preexisting hypertension.

Pathogenesis

What is the pathogenesis of accelerated hypertension? What is the mechanism of the vascular damage and progressive downhill course? There are two hypotheses: the pressure hypothesis and the renin hypothesis.

Let us examine the evidence for the pressure theory. First of all, accelerated hypertension usually develops in those patients whose blood pressure is persistently high. Raising the blood pressure in animals with experimental hypertension by saline injections can produce vascular lesions of fibrinoid necrosis.[1] Lowering the blood pressure in man or animals with antihypertensive drugs may halt or reverse the accelerated phase. In rats with a clip on one renal artery, the opposit kidney is subjected to the high pressure, and shows evidence of vascular damage, while the clipped kidney is protected and undamaged. Yet the local renin concentration is much higher in the clipped kidney. Furthermore, in the early stages of accelerated hypertension renal biopsies have not revealed fibrinoid necrosis and in a few cases there are no renal lesions at all.[3]

Obviously, there must be other factors besides pressure, since occasional patients whose blood pressure is markedly elevated for many years, never progress to accelerated hypertension. The high prevalence in negro males suggests that genetic and sex factors play a role.

The other hypothesis is that kidney damage precedes the acceleration of the hypertension. The renal vascular damage results in the release of a pressor substance, renin, which in turn accelerates the hypertension and the vascular damage. Certainly most patients with accelerated hypertension have evidence of renal damage, and many have elevated blood renin concentrations.[4] Injections of huge doses of pig renin and aldosterone to saline loaded rats produces a malignant form of hypertension.[5] In both man and animal a renovascular lesion can produce accelerated hypertension, presumably through release of renin, and correction of the lesion can abolish the hypertension.

Other evidence is at variance with this hypothesis. Accelerated hypertension has been present in patients with minimal renal lesions. Although usually elevated, plasma renin concentrations may be normal in accelerated hypertension.[4] Renin levels may even be higher in normotensive subjects, who are sodium depleted, have cirrhosis of the liver or salt losing nephritis.[6,7] In the latter subjects, despite poor renal function and elevated renin and aldosterone production, the blood pressure is usually normal. Moreover, treatment of patients with benign hypertension with diuretics may lower the pressure and abolish symptoms yet increase the blood renin concentration.[4]

Intravenous infusions of renin or large doses of angiotensin in dogs or rabbits for as long as a month have not produced accelerated hypertension.[8,9] In fact, tachyphylaxis develops to large doses of angiotensin, and the blood pressure eventually returns to normal.[9] Nevertheless, it seems reasonable that the elevated production of renin and aldosterone, by affecting sodium balance and blood pressure, may play a secondary role and worsen the already severe hypertension.

Regardless of the mechanism, once the accelerated phase develops in the patient with benign essential hypertension, prompt treatment is manda-

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tory to prevent irreversible vascular damage. Without therapy, the mortality rate is 70 to 90 per cent in the first year.[1]

Treatment

Accelerated or malignant hypertension is a serious life-threatening affliction. A search should be made for surgically remedial causes of acceleration, especially renovascular lesions. Preexisting hypertension may predispose to the formation of a renal artery plaque. A "hypertensive IVP" and in many cases an aortogram should be done. If a vascular lesion is demonstrated, then its functional significance must be determined. In the face of accelerated hypertension, a marked stenosis with poststenotic dilatation, a small kidney on the stenotic side and contralateral renal hypertrophy, is sufficient evidence to favor surgery. In other cases, renal vein renin concentrations, and a Howard test may be necessary to establish the functional significance of the lesion. The potential value of these tests must be weighed against the hazards in the severely hypertensive patient.

Hospitalization is advisable during the first few weeks of treatment. Careful but vigorous antihypertensive therapy should be started under the guidance of a physician skilled in the management of hypertensive patients. Sodium intake should be restricted but care must be taken to avoid serious volume depletion. Although there is considerable debate over the value of sodium restriction, in an occasional patient, especially one with poor renal function, the blood pressure responds to a reduction in sodium intake. Sodium depletion and antihypertensive therapy will reduce glomerular filtration rate and renal blood flow. Renal function is best followed by measuring the serum creatinine. The BUN may be disproprotionately increased as a result of a diminished urinary output and an increased fractional reabsorption of the glomerular filtrate in the proximal tubule resulting from volume depletion. During the early phase of treatment, the eyegrounds, cardiac status, renal function and serum electrolytes as well as supine and standing blood pressure should be evaluated daily.

Combinations of drugs are frequently necessary to treat accelerated hypertension. Except in the hypertensive crisis, the oral route of administration is preferred. Time is important. The drugs selected for treatment should have a high degree of reliability in reducing blood pressure. Guanethidine is such a drug. Chlorothiazide administration increases the effectiveness of guanethidine so that a smaller dose is necessary thus reducing side effects. An effective starting regimen is chlorothiazide 0.5 gm twice a day, guanethidine, 30 mg each day. In view of the cumulative action of guanethidine, the dose should not be increased until after 3 day of therapy. If hypokalemia is not easily controlled by potassium supplements, aldactone may be used in place of chlorothiazide. Occasionally, the addition of apresoline to the regimen may be effective. The head of the bed should be raised 8 inches to insure maximal effect of the antihypertensive drugs. A sedative or tranquillizer should be administered; phenobarbital is effective and inexpensive, and an effort should be made to ease the tensions in the patient's life.

Once the blood pressure is controlled and stabilized in the hospital, the patient may be followed at home on modified activity. The patient or a member of his family must learn to record the blood pressure in the supine and standing position. This is important for evaluating drug effect, since the blood pressure recorded in the physician's office is often much higher than blood pressures at home or at work. During the early phase of treatment, the Visiting Nurse Association nurse should visit the home once a week to review the drug administration and blood pressure measurements. The physician must review the case weekly. Frequent urinalysis, blood creatinine and electrolyte measurements are necessary.

The aim of therapy is to reduce the blood pressure to normal or near normal without producing incapacitating symptoms. Once the situation appears stable the visits to the physician can be less frequent but the physician should see the patient at least monthly during the first year.

Treatment must be continued indefinitely. After several years, the anti-hypertensive drugs may be withdrawn and, in some patients, the blood pressure will remain low. The cost of treatment in time and money is high but the rewards are great. Many patients have been rescued from certain death. The 5 year mortality rate has been reduced from 90 per cent to 30 per cent in patients with accelerated hypertension without azotemia.[10] Treatment of accelerated hypertension with azotemia is less rewarding but even in this group if the accelerated hypertension is controlled, a few patients will have prolonged survival, and many, a more comfortable life. However, in these patients, extreme caution must be observed, especially when the BUN is more than 60 mg per cent, since the danger of increasing uremia is great when the blood pressure is lowered too precipitously.

The treatment as outlined is not vigorous enough for the rare patient with hypertensive encephalopathy and rapidly deteriorating vision. In these cases intravenous arfonad or apresoline should be administered carefully in an intensive care unit with constant monitoring of the blood pressure, pulse and urine output. When the blood pressure and symptoms are adequately controlled—usually within one to two days—a switch to intramuscular or oral medication is feasible.

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"Reading Difficulties In Children" Symposium

A Symposium on "Reading Difficulties in Children" will be held Thursday, September 28 at 3:30 P.M. at Mary S. Harkness Memorial Auditorium, Yale University School of Medicine.

Invitations have been sent to ophthalmologists, pediatricians, school physisicians, remedial reading teachers, and various educators. Other physicians interested in the subject are welcome.

The symposium moderator will be Albert Solnit, M.D., Director of the Child Study Center and Professor of Pediatrics and Psychiatry, Yale University School of Medicine. The speakers will be Louis Cooper, Ph.D., Professor of Education, University of Connecticut; Herman Goldberg, M.D., Assistant Professor of Ophthalmology, Johns Hopkins University School of Medicine; and Ethelyn H. Klatskin, Ph.D., Assistant Professor of Psychology (Pediatrics), Yale University School of Medicine.

Sponsoring organizations are the Connecticut State Medical Society, the Connecticut State Department of Education, and the Connecticut Association for Reading Research. The Symposium has been planned by the Society's Committee on Eye Care and Section on Ophthalmology.

Heart Block In Coronary Vascular Disease

Doris J. W. Escher, M.D.

The reported incidence of complete heart block in acute myocardial infarction ranges from one to ten percent. New constant monitoring methods suggest that the higher incidence is more realistic, but because episodes may be transient and clinically unobtrusive, they have been unrecorded, except by chance, in the past. Ninety percent of known survivors revert to sinus rhythm within two weeks and their subsequent prognosis does not differ from those who are not observed to have this arrhythmia. While the incidence of significant heart block in acute occlusion may not exceed ten percent, antecedent occlusion is reported in up to twenty-five percent of patients with acquired high grade block. Postmortem studies, however, suggest that major coronary artery disease is present in less than fifty percent of patients with heart block and that more commonly all that is seen are microscopic areas of fibrosis which may be scattered througout the myocardium or limited to the areas of the conduction system.[1,2] The ages of patients with acquired heart block range from the second to the tenth decade, but over fifty percent occur in the seventh and eighth decade.

Heart block is associated with occlusion of the right coronary artery and infarction of the posterior wall approximately three times as often as with the left coronary or anterior wall. This is because in about ninety percent of patients, it is a branch of the right coronary artery that supplies the A-V node. In occlusions of the left coronary artery, with anterior or anteroseptal infarctions, heart block may be due occasionally to occlusion of the left circumflex artery when it supplies the A-V node. More commonly it is associated with septal damage affecting the conduction system, particularly if there is coexistent disease of the right coronary. The mortality rate in anterior wall infarction with heart block is approximately twice as high as that in posterior wall infarction with heart block. When the idioventricular complexes remain of normal duration in acute infarction, the prognosis for life is improved.[2] The mechanism precipitating Stokes-Adams seizures appears to be asystole in about seventy-five percent of the patients, and ventricular tachycardia or fibrillation, alone or in combination with asystole, in the remainder. The incidence of these episodes in heart block in general has been reported variously as thirty-five to sixty-seven percent. Prognosis for life is curtailed when Stokes-Adams seizures occur, particularly in the acute coronary where death rates in reported series have ranged from thirty-five to one hundred percent. In chronic or intermittent heart block, spontaneous recoveries from repeated episodes of less severe intensity occur frequently. At times, syncopal episodes may be the first and only indication that patients, thought to be in sinus or other stable conducted rhythms, should be investigated for the possibility of intermittent high grade heart block.

Ventricular bradycardia, in patients with acquired heart block, is associated with a drop in cardiac output to as low as fifty percent of the normal. Of this, ten to thirty percent is due to loss of synchronous atrial transport in complete heart block and the remainder to ventricular dysfunction from varying degrees of distortion of the conduction sequence and myocardial disease. The more severely affected patients have a lower cardiac output to begin with, are unable to increase this except by an increase in ventricular rate and even with artificial pacing at normal physiologic rates, never reach a normal output. Patients with lesser degrees of disease, may have only a moderate reduction in cardiac output at low heart rates and approach normal with artificial pacing at normal heart rates. These patients, at fixed low or normal heart rates (40-100/min.) are able, also, by an increase in stroke volume, to increase their cardiac output in response to exercise. At higher artificial heart rates (80-140/min) the cardiac output in both groups of patients will again decrease. This will occur earlier in the rate range when myocardial disease is more severe, the energy cost of a tachycardia less tolerable and the loss of the atrial contribution in the foreshortened diastole more important to ventricular filling.[2-4] In the acute coronary, these effects are exaggerated. As the ability to increase the cardiac output by an increase in stroke volume is lost, it becomes increasingly urgent to effect an increase in heart rate in order to improve the cardiac output, bring the patient out of congestive failure, support the blood pressure and maintain urinary output.

The treatment of heart block is aimed at the treatment and prevention of Stokes-Adams attacks and of heart failure and its sequela. Drug therapy may be effective in patients with less damaged

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hearts, particularly when they are not prone to major Stokes-Adams seizures. If their mechanism for syncope is ventricular fibrillation, if they are subject to ventricular irritability, if heart failure is severe and if digitalis increases their heart block, then they are better treated by artificial pacing.

The most effective drugs are the sympathomimetic amines, principally ephedrine, epinephrine and isoproterenol. The first two may exert a vasopressor effect. Their principal action in heart block is to accelerate the idioventricular pacemaker, but they also exert an inotropic effect on the myocardium and may facilitate A-V conduction. They are contraindicated in the presence of, or if they precipitate irregular or rapid ventricular ectopic activity. Ephedrine, the least effective, is administered orally, usually 30 to 60 mg. every four hours. Epinephrine is given subcutaneously or intramuscularly in doses of 0.3 to 0.6 cc of a 1:1000 solution or intravenously 0.5 mgm in 500 cc of isotonic glucose, administered with caution. In asystole, 1 cc of a 1:1000 solution may be given by intracardiac injection. Isoproterenol is by far the most effective of the three. It may be administered sublingually in doses ranging from 5 to 10 mg, three times a day to 20 to 30 mg every two to four hours. A commonly effective schedule is 10 to 20 mg four times a day or every four hours. Most patients can tolerate omission of the night dose, some cannot. The subcutaneous dose is 0.2 to 0.4 mgm, administered as often as necessary and tolerated. Intravenously, a solution of 1 to 5 mgm in isotonic glucose may be used with the drop rate carefully titrated to the patient's response. Some patients become increasingly unresponsive to these drugs, even at the higher doses and must turn to artificial pacing. In the acute coronary, their arrhythmic effect may be accentuated.

Atropine is rarely useful in accelerating the ventricular rate, requires large doses and is poorly tolerated because of its side effects. The corticosteroids are indicated only in the presence of an acute inflammatory reaction when doses up to 100 mg of prednisone per day may be given brief trial. The use of 0.16 sodium lactate or lowering of the serum potassium by chlorothiazide is generally ineffective in effecting an increase in ventricular rate. Digitalis or the antiarrhythmic drugs, such as procainamide or quinidine are more likely to reduce the ventricular rate or enhance, rather than allay, disturbances of rhythm when applied for this purpose.

When a patient in heart block is controlled by artificial pacing, the cardiac glycosides or any of the antiarrhythmic drugs are no longer contraindicated and may be used to great profit. Digitalis may be administered freely for its inotropic effect or for the control of supraventricular tachycardias in patients prone to develop heart block or asystole at therapeutic doses. The antiarrhythmic drugs, including propanolol may be used to suppress ectopic ventricular rhythms without concern, as the response to pacing is maintained in spite of depression of spontaneous ventricular rhythmicity at therapeutic doses. This combined approach greatly broadens the protection afforded the patient and extends the useful range of both the pharmacologic and electronic modes.

Artificial cardiac pacing is probably the best therapeutic approach to the significantly or dangerously symptomatic patient with complete heart block and Stokes-Adams seizures or with a low cardiac output resulting in cardiac, renal or cerebral decompensation. A problem in the past has been to match the equipment appropriately to the patient's underlying rhythm.

In complete, or stable 2:1 heart block, or a slow sinus mechanism, fixed rate asynchronous pacing eliminates Stokes-Adams seizures due to asystole and virtually eliminates the appearance of ventricular tachycardia and fibrillation secondary to ventricular bradycardia. The imposed rhythm, at normal or, if necessary, at transiently increased heart rates of up to 140 beats/min. also suppresses ventricular extrasystoles, reduces the possibility of conflict between spontaneous and artificial impulses and improves cardiac function. This same approach may be applied to over-ride and suppress multiple or multifocal ventricular extrasystoles in patients without heart block. In patients who revert to sinus rhythm or supra-ventricular conduction during fixed rate pacing, competition ensues and ventricular contraction is initiated by whichever stimulus arrives first in a nonrefractory period. In most instances this appears to cause no overt difficulty. Occasionally, however, the irregular rhythms that result are disturbing to the patient, may effect cardiac function and rarely may precipitate ventricular tachycardia or fibrillation when a succeeding impulse from either source falls on the hypersensitive zone of the T wave of the preceding beat. This last complication is seen most often in sick patients, particularly the recent coronary or those who are postoperative from cardiac surgery or anoxic or acidotic for any reason.

The problem of competition is, at present, being solved by the development of demand systems that will provide effective contractions only when the patient is bradycardiac or asystolic. The first unit applicable in this fashion was the synchronous pacemaker which requires an atrial sensor as well as a ventricular pacer electrode. This instrument was designed originally to function as an electrical substitute for a damaged A-V conduction system. By providing a ventricular contraction synchronized to follow an atrial stimulus at a normal interval, it took advantage of the atrial contribution to ventricular filling and was responsive to physiologic needs through the normal mechanisms altering the atrial rate. Inbuilt blocking circuits limit the response to sinus or supraventricular tachycardias and keep the ventricular rate within normal limits. If the atrial signal is lost or sinus bradycardia ensues the pacemaker is designed to maintain a reasonable ventricular rate by dropping into fixed rate pacing. This system, however, requires a stable atrial rhythm for optimal function and is poorly responsive to the intrusion of ventricular extrasystoles or to nodal rhythms or atrial fibrillation.

Two other types of pulse generators have been designed which, because they are based on ventricular, rather than atrial sensors, can accommodate themselves to the rhythms that the P wave synchronous pacemaker cannot handle. The first of these is a modification of the P wave synchronous pacemaker in which a single electrode, applied to the ventricle, senses ventricular activity and immediately applies a ventricular stimulus. This stimulus falls in the early completely refractory period of the spontaneous QRS and is functionally inactive during any ventricular rhythm above a preset minimal normal base rate. Should ventricular bradycardia or asystole occur, the pacemaker reverts to fixed rate stimulation at this preset low normal rate. In the second system, feedback along the single electrode from a spontaneous ventricular beat blocks a stimulus output entirely unless the interval to the next spontaneous R wave is longer than that established to provide a low normal safeguard ventricular rate. Should this occur, fixed rate pacing ensues which continues until forshortened R-R intervals again block the pacemaker output. These several pulse generators for fixed rate, demand and synchronous pacemaking are now becoming available for application by percutanious transvenous routes with the generators explanted or by pervenous or myocardial routes with the pulse generators completely implanted. An additional unit has been marketed applicable either by the pervenous or myocardial route which consists of an implantable receiving coil attached to the electrode with an exteriorized pulse generator providing fixed rate pacing by induction through a coil applied to the skin over the receiver.

Several routes of application of these pacing modes have been developed. The first, and simplest, is transcutaneous thoracic stimulation by external electrodes attached to an external pulse generator. This is the usual method applied first in emergencies and is commonly available as part of most intensive care monitoring systems. It supplies asynchronous pacing at rates that can be fixed by the control of the exteriorized generator and can be set to be automatically initiated by an asystolic alarm through sensors attached to peripheral electrocardiographic leads. This method is painful because of the general galvanic response it produces; is not always effective and prolonged use should be planned only if no more direct method is available. The second method is application of percutaneous transvenous catheter electrodes to the mid-outflow or apex of the right ventricle. The three major variations of this approach are: 1) Transjugular insertion through the right or left external jugular, or if necessary, internal jugular vein, using a radiopaque catheter* inserted under fluoroscopic control to the outflow of the right ventricle, if the catheter is moderately stiff, or to the apex if it is moderately soft. Use of the brachial vein is relatively unsafe as arm motion results in catheter motion in the heart and may cause interruption of pacing or rarely perforation of the myocardium. 2) Application of a semi-stiff radiopaque catheter under fluoroscopic control to the apex of the right ventricle through specially designed Teflon needles inserted percutaneously into the femoral vein. Only limited ambulation may be allowed if this route is used. 3) The third method employs the extremely light Davis & Geck electrode** used as described by Kimball and Killip. These electrodes can neither be visualized or manipulated. They are floated into the blood stream through needles inserted in the brachial, subclavian or external jugular veins. Their course to the heart is controlled by the flow of blood and their position ascertained by constant monitoring through the V lead of the electrocardiogram attached to the exteriorized portion of the electrode. These three approaches are relatively safe, effective and offer little stress to the patient. Another percutaneous approach, to be reserved for acute emergencies, is transthoracic direct left ventricular myocardial insertion of an electrode through a special needle.*** Pacing by all of these percutaneous routes may be by the pulse generators of monitor systems but is much safer when applied by isolated transistorized battery powered units. These small generators are manufactured by several companies in the asynchronous mode and by several in demand modes. All of these companies also manufacture completely implantable units for electrodes, placed by thoracotomy, directly on the myocardium.**** Most of the companies have transvenous modifications of their completely implantable designs. These do not require either thoracotomy or general anesthesia and are particularly satisfactory for the elderly, the sick and the recent coronary.[5,6]

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* United States Catheter & Instrument Co., Glen Falls, N. Y. or Electro-Catheter Co., Linden, New Jersey.

** Davis & Geck Division of American Cyanamid Co., Danbury, Connecticut.

*** Electro-Catheter Co., Linden, New Jersey.

**** Medtronic Inc., Minneapolis, Minn., Cordis Co., Miami, Florida, Electroydne, Westwood, Mass., General Electric, X-ray Dept., Milwaukee, Wisconsin, American Optical Co., Chelsea, Mass., and Airborne Instruments Laboratory, Mellville, L. I., N. Y.

The routine of approach to a patient in symptomatic heartblock will vary with the urgency of the situation. Most urgent is the patient with major, recurrent Stokes-Adams seizures or the recent coronary with bradycardia, shock, heart failure or Stokes-Adams seizures of any degree of severity. Treatment for the syncopal episodes should be initiated immediately by closed chest transcutaneous stimulation. At times, a sharp blow to the anterior chest wall will shock a patient out of ventricular asystole or fibrillation. As soon as possible, a percutaneous transvenous catheter should be passed to the right ventricle and pacing initiated by fixed rate asynchronous stimulation if block is complete or the patient intrudes ventricular premature systoles that can be over ridden by an increase in paced rate. When available, in unstable rhythms, demand pacing is preferable. A patient already in ventricular fibrillation cannot be paced until counter shock is used to re-establish a slow or coordinate rhythm. Defibrillation and pacing are relatively difficult to effect and maintain in the anoxic or acidotic patient and closed chest message, airway care and oxygen and base supplement may be required as part of the therapeutic approach even before pacing is established. Pacing by a pervenous route, femoral for a short term or jugular for long, should be continued as long as the patient is unstable and until it is evident either that the incident is transient and the pacemaker may be removed or that the situation is fixed and permanent pacing should be considered. Electrodes passed by the femoral or brachial route are usually removed after 7-10 days because of the risk of thrombosis or motion dislocation of the electrode. Those passed by the jugular route may remain in situ for months to years if necessary, with due care given to the potential incidence of bacteremia, and are safe and stable. Catheters originally in the leg or arm, therefore, may be transferred to the jugular route if prolonged observation by a temporary route is desired. All patients with percutaneous pacing receive antibiotics usually 600,000 units of penicillin two times a day for the first 3 to 7 days of use unless the patient is diabetic or has a coexistent infectious process in which event, antibiotics are continued for the duration of use. Anticoagulants are not employed for this purpose alone but are not contraindicated if needed for other reasons.[1,5,6] Once permanent pacing is considered to be needed, it is instituted under the continued support of the temporary assembly which should remain in place but inactive, as an insurance, for the first 1 to 3 days post permanent implantation. The choice of mode and route for the permanent units will vary with the considerations given above and is individualized to the patients needs and tolerance.

The patient in chronic heart block without Stokes-Adams seizures, who is in congestive failure or who exhibits personality changes or renal insufficiency on the basis of a low cardiac output, is a less urgent problem. These patients frequently cannot be digitalized without the risk of increased bradycardia or asystole and are inadequately responsive to or unable to tolerate the sympathomimetic amines. They should be observed for a period of time under pacing by a temporary transvenous route. If they are responsive and permanent pacing seems indicated, then again, it can be done at leisure under support of the transvenous system.

Patients with shifting rhythms or intermittent block, who cannot be controlled medically, are also candidates for permanent pacing but in these patients, some mode of demand or synchronous stimulation is the method of choice. Again, trial on a temporary system is advised. As temporary pacing is not usually attempted in the synchronous mode, these patients are tested on a demand unit. The ultimate choice of synchronous vs demand modes, in the unstable patient, depends upon the stability of the sinus mechanism, the age of the patient, tolerance for the relative tachycardia that may develop and the need of the atrial transport contribution. The same consideration may be extended to the choice of asynchronous vs synchronous pacing in the patient in fixed block. As the synchronous mode will shortly be available as a transvenous method, thoracotomy may cease to be a factor in the choice.

A problem in both temporary and permanent transvenous pacing, is the skill and care with which the electrode is applied. Placement by anatomic orientation alone is inadequate. It is important that the threshold to stimulation is as low as possible. In the temporary pervenous electrodes, a current in excess of 1.5 mA, indicates a suboptimal position. In the implantable transvenous systems, threshold varies with the type of electrode used but should not exceed 2.5 mA with any installation and may be under 1.5 mA with some. This is more urgent in the implantable systems, myocardial or transvenous, where the ability to alter current in response to needs is limited or absent and where a significant increase in threshold may occur within a period of a few weeks after insertion. In the temporary systems, less attention need be paid to threshold as it is possible to increase current by external control if the catheter is poorly positioned. Indeed, at insertion, if the patient is asystolic, the generator should be connected and set immediately to a relatively high current, in order to capture the heart as soon as possible. Later, further manipulation may permit a reduction to an optimal level. High currents with a poorly fixed catheter and shifting thresholds pose a certain amount of danger, particularly in the recent coronary, unless a demand pacemaker is used. In these cases, in particular, the excessive stimulation may incite an arrhythmia if it should fall in a vulnerable area of a preceding spontaneous beat.

A limiting factor in all implanted assemblies is still the problem of battery replacement. Most systems exhibit a significant number of instances of battery exhaustion by two years of use, though many are rated and perform for three years. A program of followup on these patients, is important, with attention paid to signs of instability. Functional breakdown in either the electrode of the pulse generator of any type of system still occurs but is decreasing in incidence. The physician undertaking responsibility for installation of these systems should acquaint himself with details of the diagnosis and rectification of these failures. X-rays will frequently demonstrate electrode fracture and sometimes fluoroscopy or cineangiography will reveal breaks or displacements not appreciated on plain films. A study of the electrocardiogram will indicate whether or not the pacemaker stimulus persists and whether the failure to pace is real or based upon intrusion of an underlying conducted rhythm. Each of the systems of pacing brings with it, special consideration of its own in regard to the normal or aberrant response. These, and details of repair, exceed the scope of this review and should be sought in specific publications.[7]

Specific statistics on the safety and value of artificial pacing in the treatment of heart block are in constant flux. It is fair to say, however, that the mortality rate of the patient with an acute coronary complicated by heart block is better than halved when pacing is employed. Since death by a Stokes-Adams seizure need no longer occur, the patient's life span becomes governed instead by the general course of his underlying cardiac pathology or by intercurrent non cardiac factors. Symptom free survivals of four to eight years are now on record of patients who were admitted originally in pre terminal states because of Stokes-Adams seizures. Many of these, in addition, have recovered from congestive failure, uremia or cerebral confusion. While some deaths have occurred due to further coronary episodes, to pacemaker failures, or to congestive failure, a significant number have been due to cancer, infections, uremia or other non cardiac causes.

The value, therefore, of artificial pacing in the treatment of heart block in the acute coronary, or in acquired heart block of any cause, is clear and has completely changed the course and prognosis of patients with this lesion.

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Risk Factors In Coronary Vascular Disease

Joseph T. Doyle, M.D.

Coronary heart disease is by all odds the major threat to life for the American male.[1] Efforts to prevent or to ameliorate coronary heart disease have been frustrated by the difficulty of elucidating the etiology and pathogenesis of a disorder almost certain not to have a single and unique cause; the incubation period of which is measured in decades; which is undetectable by ordinary clinical methods until the appearance of its late ischemic complications—all too often sudden death; and for which there is no satisfactory experimental model.

It is generally supposed that atherosclerosis of the coronary arteries is responsible for the syndromes of myocardial ischemia.[2,3,4] Since the composition of the atheromatous plaque is virtually identical with that of the circulating blood lipids, it has been further supposed that atherogenesis reflects an as yet unexplained disorder of fat metabolism. On the other hand, the acute occlusive phase of atherosclerosis is generally thought to be precipitated by thrombus formation over an atheromatous ulcer. It has, therefore, been proposed as a unifying hypothesis that thrombosis may, indeed, be the initial as well as the terminal event in atheropoiesis.[5,6,7] A minority feel that the mechanistic aspects of coronary heart disease have been overemphasized and that a frequent pathogenic factor is the hypoxiating effect of endogenous catecholamines on a myocardium rendered vulnerable by poor physical conditioning.[8] The paradox that myocardial infarction may *cause* coronary artery thrombosis is not easily refuted when it is appreciated that a thrombus is not regularly found in fatal cases until 12 to 24 hours after the onset of evidences of acute myocardial ischemia.[9,10]

Against this background of ignorance and conflicting theory vigorous efforts have nonetheless been made to identify quantifiable characteristics associated with unusually high rates of coronary heart disease. The justification of these efforts has been the hope that sufficient information might be gained to permit the application of empirical measures to control coronary heart disease, just as nonspecific hygienic measures proved so effective in reducing the rates of many acute infectious diseases prior to the chemotherapeutic era. Many sources have been utilized to gain our present imperfect albeit considerable knowledge of the natural history of coronary heart disease.

Mortality statistics have provided an approximation of the dimensions of the problem although the accuracy of the death certificate can be questioned on many grounds and furthermore do not reflect morbidity.[11]

The retrospective study of coronary heart disease which starts with the patient identified as having this disorder is, of course, the classical approach. Useful though this technique has proved for the clinician it is productive of little statistically valid information. There are many reasons for the shortcomings of the retrospective clinical approach: the population of patients is selected by the very fact of disease; numerous factors determine where and at what stage of their disease medical help is sought; the size and the characteristics of the universe from which the patients are derived are usually unknown and undefined; there are numerous biases inherent in the recall of events prior to the onset of a catastrophic illness. Furthermore, clinical techniques although admirably suited to the needs of immediate patient care, are rarely adapted to statistical assessment and usually lack standardization, reproducibility and comparability. Few clinic populations contain enough patients and matched control subjects to permit accurate estimates of disease rates or comparisons between subgroups categorized by various characteristics. Autopsy studies have, of course, the same handicaps.

Prevalence or incidence rates for coronary heart disease are nonexistent since the disease is not reportable, although a few efforts have been made to collect such information on a limited basis. Ad hoc studies such as the National Health Survey have been required to estimate prevalence rates.[12]

The most effective approach to the study of coronary heart disease has been the prospective epidemiological study which permits accurate measurement of prevalence as well as of incidence, that is the rate of appearance of new disease. Ideally, a large and well defined population is induced to permit itself to be studied over a long period of time. Clinical and laboratory investigative methods are rigorously standardized and their sensitivity and specificity well appreciated. Diagnostic criteria are meticulously developed and standardized. No therapeutic manipulations are undertaken and are, in-

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deed, theoretically undesirable. The study population is large enough so that meaningful comparisons can be made between subgroups according to different biological and demographic characteristics. The prospective epidemiological study is not without important shortcomings. The necessity of employing standardized methods which remain constant year after year imparts an inevitable rigidity. Secular changes in the biological characteristics of the disease under study may escape recognition. Statistical methods for assessing the influence of changing intensity of risk factors do not exist. The required period of surveillance is long and may well exceed the lifetime of the investigators. Results accumulate slowly and are rarely dramatic or newsworthy. The recruitment of a suitable study population and of competent technical staff is difficult and the continued maintenance of such an organization very expensive. Thus, although it is from prospective epidemiological studies that our best information on the natural history of coronary heart disease has been derived, few such studies have been undertaken.[13-18]

From all these sources of information it has been possible to assemble a fairly detailed description of coronary heart disease even though we remain ignorant of its etiology and pathogenesis. It is certain that disease of the coronary arteries was recognized at least several centuries ago. Jenner correctly predicted that John Hunter's chest pains were due to coronary artery disease.[19] It is impossible to determine whether there has been an absolute increase in the frequency of coronary heart disease since the turn of the century inasmuch as the clinical picture has been well defined and commonly recognized only in the past 35 years or so, a period in which the electrocardiograph has been introduced into universal clinical application. Aside from lack of recognition of or confusion of myocardial infarction with other catastrophic illnesses, the mode of death certification prior to 1948 renders it virtually impossible to assess the frequency of fatal coronary heart disease prior to that date.[20] There do, on the other hand, seem to be very real and substantial international differences in the mortality ascribed to coronary heart disease, ranging from 300 per 100,000 in this country down to 57 per 100,000 in Japan.[21] It has seemed to many investigators that if these differences could be explained by measurable differences in the mode of life between our country and those countries less afflicted by coronary heart disease, powerful means of prevention might be devised. Unfortunately, so many uncontrollable variables are involved in these comparative studies that this goal has not been achieved. Of great interest and quite unexplained are large differences in mortality from coronary heart disease reported between some states in this country.[22]

Although in the United States women and men age for age have equal degrees of atherosclerosis, women have far lower rates of coronary occlusion.[23] Estrogenic activity does not explain this difference. The only controlled study of the effects of oophorectomy well before the natural menopause failed to show an excess of coronary heart disease in castrated women.[24] Estrogens do not protect men against recurrent myocardial infarction.[25] The rate of coronary heart disease in women appears to be a function of increasing age inasmuch as there is no sharp upward inflection after the menopause.[26] Where the rate of coronary heart disease is low there is little sex differential.[27]

In all susceptible populations the incidence of coronary heart disease rises with increasing age due presumably to the longer operation of pathogenic factors.[13,14]

It is doubtful that racial differences in the rate of coronary heart disease reflect true constitutional differences. The incidence in migrant groups tends to approach that of the dominant population. For example, the rate of coronary heart disease in Japanese living in Hawaii is greater than the rate in Japan but substantially lower than for Japanese living in California, where the rate is nearly that of Caucasians.[21,28-30] In the rural South the rate of coronary heart disease is lower in Negroes than in whites, although poor whites and Negroes have about the same rate.[27] The role of genetic factors is difficult to distinguish from the effects of environment. Familial hyper-cholesterolemia does, however, seem to be one heritable trait clearly associated with precocious and severe coronary heart disease.[31]

A relationship between occupation and coronary heart disease has commonly been related to physical activity and to emotional stress. The evidence on physical activity is conflicting.[32] Vigorous physical activity probably does not protect against mycardial infarction although it is possible that it may improve the chances of survival.[33] It has long been assumed on intuitive grounds that unremitting emotional stress predisposes to coronary heart disease. No objective evidence to support this view has yet been produced. The higher rate of coronary heart disease in urban compared with rural populations could be related to occupational differences, but major self-selective factors obscure the issue.[34]

The attention of the prospective epidemiological studies has been directed primarily towards variables susceptible of objective measurement which can be related to the appearance or nonappearance of coronary heart disease. The findings of all such

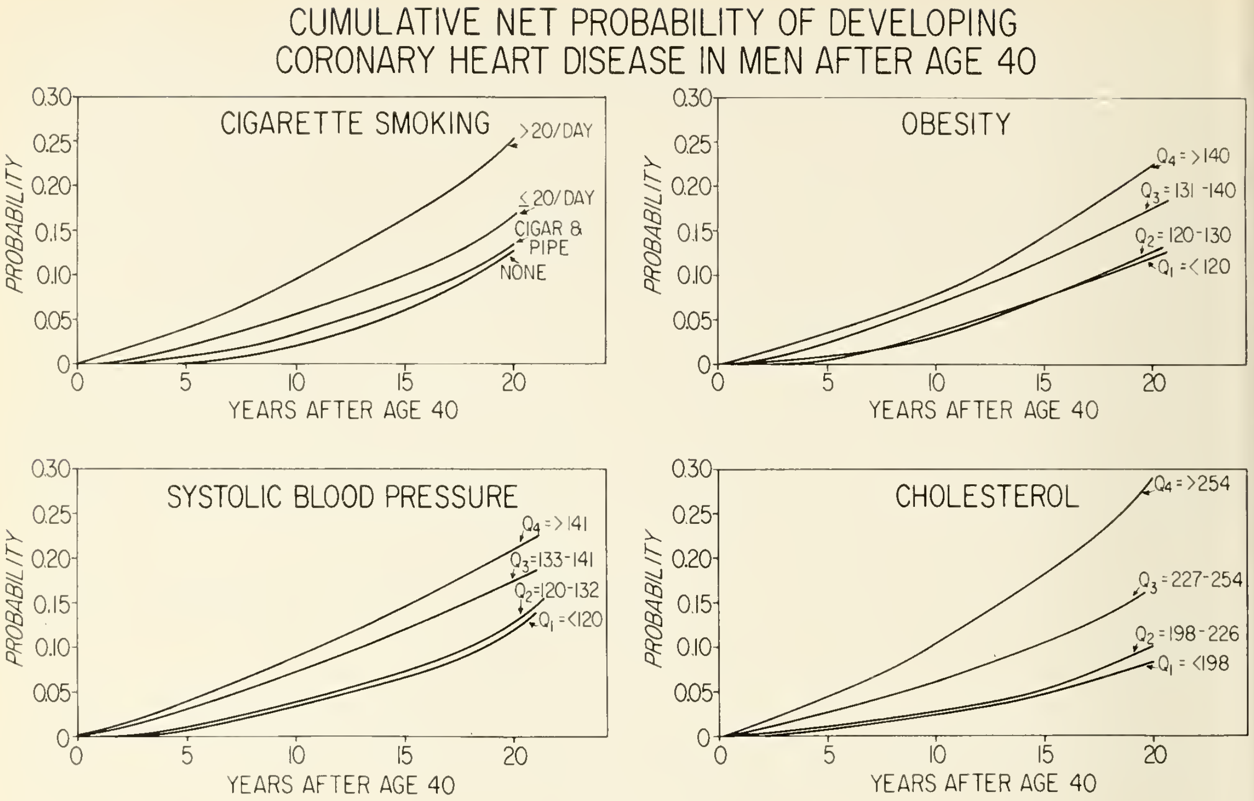

Figure 1

The contribution to the risk of coronary heart disease of four characteristics is illustrated. The mode of presentation is a modification of the life table.[35] The experience of a population of men varying in age from 39-55 years when these characteristics were first recorded and under surveillance for differing periods since that time has been amalgamated. Gradation in risk is shown by dividing the population into quartiles according to the specified risk factor.

studies in this country have been remarkably consistent.[13-18] The higher the serum total cholesterol, the higher is the rate of coronary heart disease Fig. 1).[35] There are, of course, notable exceptions and individual predictive power is poor. Thus, in the Albany Cardiovascular Health Center study, a quarter of the new events of coronary heart disease have occurred in men whose serum cholesterol concentration is below the average for the whole population. The original notion that the cholesterol level is highly correlated with the dietary fat intake has not been corroborated.[36,37] Dietary carbohydrate may play a role more important than hitherto supposed since it may cause hypertriglyceridemia.[38] The atherogenicity of triglycerides is, however, presently unknown. Overweight due to obesity has proved to be far less serious a risk than represented in the past (Fig. 1).[14] The higher the level of the blood pressure the higher is the rate of coronary heart disease (Fig. 1).[14] The mechanism involved is not clear, although it is usually presumed that high intraluminal pressures cause an increased rate of percolation of the blood lipids through the vascular tunics and thereby accelerate atheropoiesis. Of all personal habits and characteristics, the practice of cigarette smoking appears to have the most harmful effect in coronary heart disease (Fig. 1). As with all of the factors enumerated, there is a gradient of risk. Men who smoke 20 or more cigarettes daily have two and one half times the likelihood of sustaining a myocardial infarction as nonsmokers or pipe or cigar smokers while those who smoke 10 cigarettes daily are at an intermediate level of risk and those who smoke 60 cigarettes daily run a much higher risk. There is, curiously, no association between cigarette smoking and angina pectoris. Cigar and pipe smoking are, apparently, unrelated to any manifestation of coronary heart disease. Finally, ex-cigarette smokers appear to have no greater a risk of myocardial infarction that nonsmokers, an observation with important hygienic implications.[39] While it is likely that the simultaneous presence of several risk factors is associated with a substantially greater risk of coronary heart disease than that contributed by any single risk factor, it has not been possible to identify a sufficiently large number of individuals at multiple risk to make a statistically sound estimation of hazard. Indeed, in the general population it may be that fewer than one per cent, based on the findings of a large screening study, harbor multiple risk factors.[40]

As was pointed out earlier, the incentive for identifying these various risk factors is the hope that the deliberate modification or elimination of those accessible to intervention may be associated with a corresponding reduction in the incidence or amelioration of coronary heart disease. Thus, it has been estimated that a 15% reduction in the serum total cholesterol concentration might be attended by as much as a 35% reduction in the incidence of coronary heart disease, all other factors remaining constant.[41] The difficulties of mounting a scientifically controlled program of coronary risk factor modification are self-evident. The interest of the public in such efforts is intense. There are doubtless few health-conscious individuals in the United States who have not already in various ways modified their living habits in the hope of avoiding a heart attack who would willingly serve as controls in any sort of mass study of risk factor modification. Whether our present imperfect knowledge justifies the uncritical wholesale application of those measures thought to be helpful is a question most difficult to answer. It does seem unlikely that such programs will provide interpretable results. It is also questionable that the application of these empirical measures to an adult population, most of whom may be preseumed to have advanced atherosclerosis, will prove worthwhile. The available evidence indicates that atherosclerosis begins in infancy. Perhaps our preventive efforts should be directed towards the young. Difficult decisions confront the centers of medical excellence now mandated by law to establish regional programs to mitigate heart disease, cancer and stroke.

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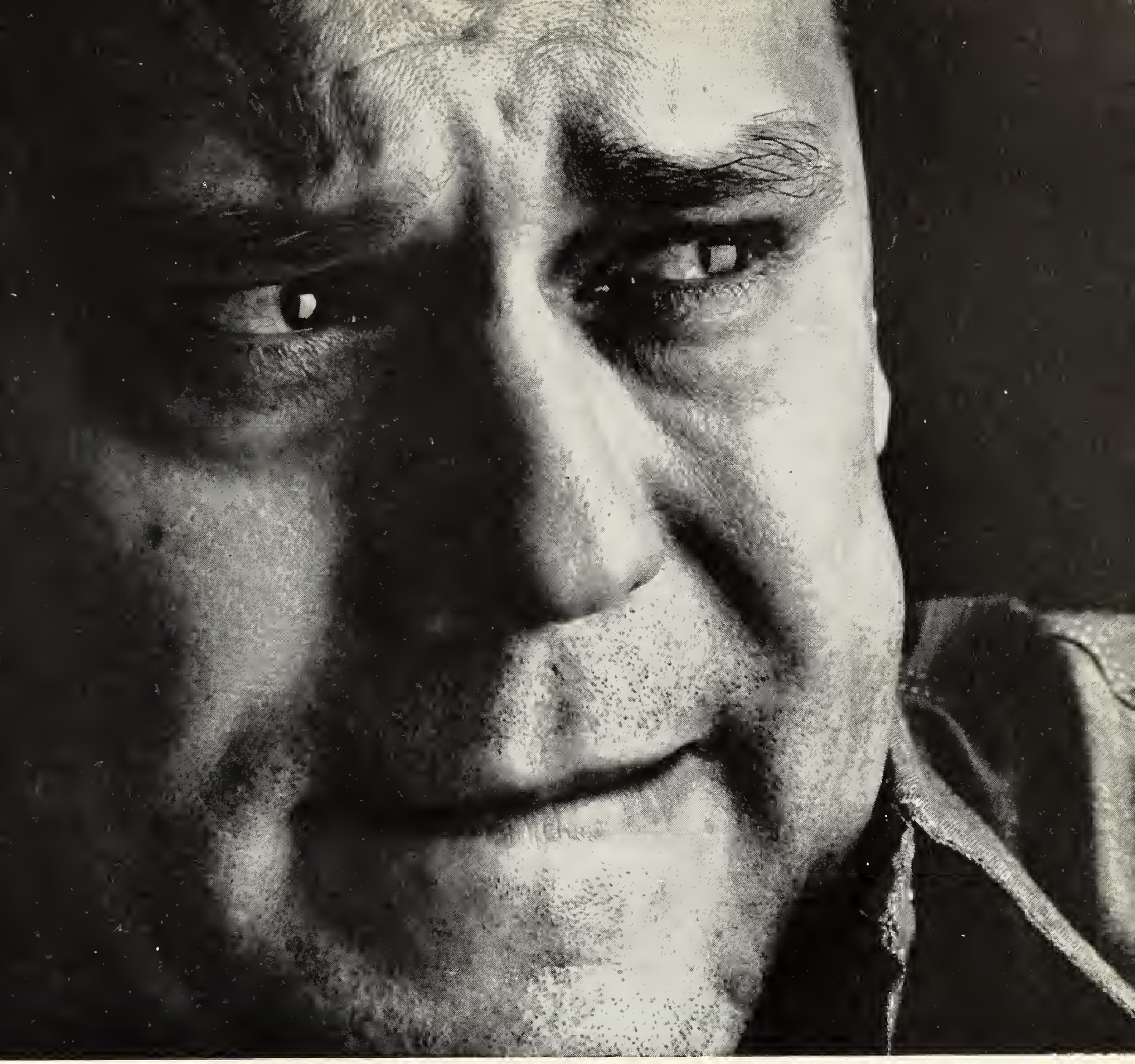
Society's Section On Ophthalmology Announces Meeting

Andrew S. Wong, M.D., President of the CSMS Section on Ophthalmology, has announced that there will be a fall meeting of the Section on Wednesday, October 11, 1967, at New Haven.

The meeting will open with an afternoon program, to be held at the Eye Clinic of the Yale-New Haven Medical Center, starting at 1:30 P.M. Robert Hollenhorst, M.D., Professor of Neuro-ophthalmology at the University of Minnesota and the Mayo Clinic, will conduct a clinic in neuro-ophthalmology, assisted by Thomas Walsh, M.D., Assistant Clinical Professor of Neuro-ophthalmology at the Yale School of Medicine. At the conclusion of the clinic presentation, a brief business meeting of the Section will take place at 4:30 P.M.

In the evening, starting at 6:00 P.M. at the Park Plaza Hotel in New Haven, there will be a reception and dinner in honor of Dr. Hollenhorst, following which he will speak on "Retinal Arterial Occlusive Disease as a Manifestation of Systemic Vascular Disorder."

Any physician interested in attending the reception and dinner is asked to make reservations before October 3 with: Daniel M. Taylor, M.D., Secretary, CSMS Section on Ophthalmology, c/o Grove Hill Clinic, New Britain, Connecticut.



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Contraindications: Infections caused by nonsusceptible organisms; history of penicillin sensitivity.

Warnings: Acute anaphylaxis (may prove fatal unless promptly controlled) is rare but more frequent in patients with previous penicillin sensitivity, bronchial asthma or other allergies. Resuscitative (epinephrine, aminophylline, pressor amines) and supportive (antihistamines, methylprednisolone sodium succinate) drugs should be readily available. Other rare hypersensitivity reactions include nephropathy, hemolytic anemia, leucopenia and thrombocytopenia. In suspected hypersensitivity, evaluation of renal and hematopoietic systems is recommended.

Precautions: In suspected staphylococcal infections, perform proper laboratory studies including sensitivity tests. If overgrowth of nonsusceptible organisms occurs (constant observation is essential), discontinue penicillin and take appropriate measures. Whenever allergic reactions occur, withdraw penicillin unless condition being treated is considered life threatening and amenable only to penicillin. Penicillin may delay or prevent appearance of primary syphilitic lesions. Gonorrhea patients suspected of concurrent syphilis should be tested serologically for at least 3 months. When lesions of primary syphilis are suspected, dark-field examination should precede use of penicillin. Treat beta-hemolytic streptococcal infections with full therapeutic dosage for at least 10 days to prevent rheumatic fever or glomerulonephritis. In staphylococcal infections, perform surgery as indicated.

Adverse Reactions (Penicillin has significant index of sensitization): Skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported (see "Warnings").

Composition: Tablets—125 mg. (200,000 units), 250 mg. (400,000 units), 500 mg. (800,000 units); Liquid—125 mg. (200,000 units) and 250 mg. (400,000 units) per 5 cc.

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THE PRESIDENT'S PAGE

Health Care For The Body Politic

More family doctors, you say? More nursing personnel? More care for any age group? What is really the need, and who should meet it?

With the advances in medicine and the increase in population, the health of the public has become—and will continue to be—a popular vehicle in the political arena and among voluntary lay agencies. It would seem fitting that investigative, planning and operational undertakings should also have the benefit of some professional and practical guidance. Has the dust from the grindstone of individual patient care befogged our view of the broader health care problem? Let's parallel our care of the individual with the needs of the "body politic."

Prenatal and obstetrical care help insure a good start for the individual.	The health needs of the populus must be analysed prior to careful planning of the birth of a sound program.
Periodic checkups help to keep the baby or adult well to avert serious illness.	Proper supervision helps maintain efficient operation and avoid trouble.
Predictable diseases can be avoided by immunization, sanitation measures, etc.	Various mechanisms, like internal audits, can anticipate and protect against predictable troubles.
When disease strikes, it must be combatted by expert personnel and most modern armamentarium.	Any breakdown or deficiency must be attacked and corrected by the most up-to-date equipment and efficient trained personnel.
When the ravage of disease leaves some impairment, a rehabilitation program is undertaken to utilize the individual's faculties to the full.	When ill-considered laws and other road-blocks like lay directives and undue taxation obstruct the health care of the public, a new appraisal and revised program must be promulgated.
The physician cares not just for the body, but also for the spirit of the person.	The program must be concerned with the physical, mental and financial well-being of people but also should be motivated and operated by a humanitarian spirit.
Nature has provided that the body die—whereupon it is disposed of.	Laws, organizations, and even programs tend to continue to exist—though they no longer live. They too should be allowed to die.

Since it is our chosen duty to watch over the individual, we should—each of us—watch over these individuals collectively as well. We need not do all the work. We need not seek the power, nor demand the glory.

How, then? Leaving much to your imagination and ingenuity, I will offer but a few suggestions. We must always remember that our first consideration is the health care and welfare of the people of Connecticut. An attitude of cooperation rather than competition should be fostered in our relationship with all voluntary agencies. Down should come the spiked iron fence that has been wrought between the ivory tower and the wheat field. With the demand for increased quantity of medical care we must insure that high quality is maintained—partly through insistance that medical decisions are made only by medical doctors.

The cost can be kept down by efficiency methods in office and hospital, by pooling help and equipment, by group practice and appropriately organized health care centers, by avoiding "middle men" and expensive bureaucracy, by utilizing competitive pre-payment agencies and discouraging the expensive "free" care through the government.

The legislators who represent your area want your help and advice. Get to know and help them now; don't wait until you want something from them! Take an active part in COMPAC. It took a lot of Egyptians to build a pyramid.

In his Presidential address, Dr. Orvan Hess said: "It would seem wise that less energy be wasted on fear of encroachment of this type of socialized medicine and more of our energy be channeled to the guidance of existing forces toward the furtherance of a truly AMERICAN HEALTH SYSTEM, with built-in flexibility to accommodate the diversified needs of our communities."

E. Tremain Bradley, M.D.

FROM THE GENERAL MANAGER'S OFFICE

William R. Richards, m.d., *General Manager*
160 St. Ronan Street, New Haven, Conn.
Telephone 865 0587

Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

IMPORTANT NOTICE

Re: CSMS—Sponsored Overhead Expenses Insurance Plan

Members of the Society are advised that, effective November 1, 1967, there will be a 12 per cent reduction in premium rates for members enrolled in the Overhead Expense Plan who are in the age bracket 40-69 years. This follows close on the heels of last year's improvement in the Plan which gave a similar reduction in premium to policyholders in the under age 40 group. Also, members can now apply for up to $1,500/month coverage, an increase of $500 over the previous maximum.

The CSMS Committee on Medical Economics and Insurance has several times commended Group Insurers, Inc., New Haven, administrators of the Plan, for their continuing efforts to increase benefits and reduce cost since the Plan was first offered to members, under the sponsorship of the Society, in 1960. Seven distinct major improvements have been made in the policy which was offered originally. We are informed by the administrators that a new re-enrollment drive in connection with these announced changes will be launched during the period September 1 through October 31, and that liberal underwriting will be available to CSMS members while the drive is on. Those not presently having insurance protection of this type or of this high quality would do well to examine carefully the brochures which will be mailed out after Labor Day.

SUMMARY OF ACTIONS COUNCIL MEETING

Wednesday, July 26, 1967

I. Attendance

Present in addition to the Chairman, Dr. S. J. Martin, were: Drs. Bradley, Gardner, Grendon, Polivy, Brandon, M. Caplan, Fabro, Hess, Rogol, Cramer, Egan, Abbot, Spitz, Hastings, Shepard, Ayres, Nolan, Johnson, Pelz, Palomba and Roch. Also present were: Mrs. Lindquist, Mr. Norbeck (AMA), Dr. Friedberg (Chairman of Legislative Division) and Dr. Richards.

Absent were: Drs. H. Caplan, Jacobson, Jr., Grant, Petrie and Wilson.

II. Routine Business

Report Of CSMS Delegate To MMS

It was VOTED to distribute copies of the report of the CSMS Delegate to the Massachusetts Medical Society, E. Tremain Bradley, to all members of the Committee on Hospitals as information. The report had been accepted by the Council on June 15, 1967, and is on the proceedings of the 186th Annual Meeting of MMS, Boston, May 15, 1967.

COMPAC

Frank K. Abbot, Waterbury, Chairman of the newly-appointed Ad Hoc Committee on Liaison with the Connecticut Medical Political Action Committee, reported that members of the Ad Hoc Committee had attended a recent meeting of the COMPAC Board of Directors and hoped to have constructive recommendations to make to the Council in the near future. At this time, however, no definitive report was presented.

Date Of Next Meeting

It was determined that no meeting would be held in August, unless warranted by the urgency of one or more items of business, and that the date of the next meeting will be Thursday, September 14, 1967.

III. Old, New And Special Business

Report—Committee On Maternal Morbidity And Mortality

Held over from the June 15 meeting, the report of this Committee on the subject of admitting surgical cases to obstetrical floors was presented and discussed. It was VOTED to receive the report as information, and with thanks. In essence, the report recommended that the so-called "pilot" program of admitting clean gynecological cases to obstetrical floors continue to be limited to patients of qualified obstetrician-gynecologists and *not* be expanded to include general surgical patients of non-specialists in obs-gyn (as advocated by the CSMS House of Delegates on April 25, 1967). It was further VOTED to direct the Chairman of the Council to appoint an Ad Hoc Committee which, after consulting with representatives of Connecticut chapters of American Board Surgeons and Obstetrician-Gynecologists, is to formulate new guide lines for the program in accordance with the resolution adopted by the House of Delegates on April 25, and, thereafter, to discuss the entire matter with the State Commissioner of Health and present the new guidelines to him for consideration. The Chairman appointed the Ad Hoc Committee as follows:

Norman H. Gardner, East Hampton, Chairman
J. Alfred Fabro, Torrington
Payson B. Ayres, Greenwich

Resolution—Public Education Program On Title XIX (Medicaid)

It was VOTED to adopt a resolution on this subject as follows:

Whereas: Title XIX of P.L. 89-97 has now been fully implemented in Connecticut by the 1967 General Assembly; and

Whereas: Certain provisions of the Connecticut Title XIX Program are peculiar to this State, and are at variance with those adopted in other states; therefore be it

Resolved: That the Council request the Society's Public Relations Division to study and make recommendations to the Council concerning a CSMS-sponsored public education project to inform Connecticut residents of the rights and privileges of, and the benefits available to, eligible persons enrolled in the Title XIX (Medicaid) Program.

In adopting the resolution, it was understood that in order to make the educational program (if undertaken) factual, it would be necessary to consult with representatives of the State Department of Welfare for the purpose of making sure that all materials prepared and released by the Society are in strict accord with the provisions of the Title XIX statutes enacted by the 1967 General Assembly.

Proposal To Establish Administrative Liaison With The Connecticut State Dental Association

It was VOTED to approve a proposal to seek to establish continuing liaison with the CSDA at the administrative level, for the purpose of fostering joint consideration of legislative and similar matters of mutual interest, and to request the President E. Tremain Bradley, to arrange a meeting with the President of CSDA, Dr. William T. Barto, Jr., West Hartford, to discuss this proposal and report on the discussion to the Council.

Reports—Council's Fiscal Advisory Committee

Actions were taken on reports of the FAC as follows:

(a) It was VOTED to approve the recommendation of the FAC that Joseph J. Bellizzi, Hartford, Chairman of the Advisory Committee on School Health, be authorized to attend the 11th National Conference on Physicians and Schools (Chicago, October 4-7, 1967) as a representative of the Society, and to receive reimbursement for usual expenses incurred thereby in the amount of $250 (approx.). It is understood that Dr. Bellizzi will file an informative report on the proceedings of the Conference with the Council upon his return from the meeting.

(b)It was VOTED to approve a recommendation of the FAC that the Society sponsor a September 28 symposium on "Reading Difficulties in Children," planned jointly by the Committee on Eye Care and the Section on Ophthalmology, and contribute the sum of $250 to help defray the costs of the meeting. Co-sponsors will be the State Department of Education, which is contributing $200, and the Section on Ophthalmology, which is contributing $250.

(c) It was VOTED to adopt a motion offered by the FAC, concerning the general subject of financing and/or co-financing of educational projects of the Society, which read as follows:

"IT IS MOVED: That the Council instruct the Public Relations Director to investigate the feasibility of establishing a 'scientific funding bureau,' which would list available sources of funds from pharmaceutical and other outside sources, with a view toward calling on such sources for funds to be used to defray the costs of scientific meetings, conferences, symposia, etc., planned and conducted by the Society and its committees."

Conflict—Federal vs. State Laws re Telephone Prescribing Of Class A Narcotics

At the 1967 General Assembly, the statutes pertaining to narcotics were revised to make the telephone prescribing of Class A narcotics legal, providing the physician furnished the dispensing pharmacist with a properly-completed prescription for same within 72 hours. It is said that similar provision is made in the comprehensive revision of the narcotic control and treatment-of-addiction statutes. In correspondence and personal discussion with the President, E. Tremain Bradley, a regional representative of the Federal Narcotics Bureau has stated that the telephone prescribing of Class A narcotics is specifically prohibited under the Harrison Narcotics Act (and/or regulations thereunder), and that, hence, a physician giving such telephone orders will still be in violation of the Federal law—irrespective of whether it is now deemed legal to do so under State statutes.

It was VOTED to refer the file accumulated by Dr. Bradley on this question to the appropriate Department or Council of the AMA for opinion, and for consideration of the possibility of taking legislative activity at the Congressional level to modify the Federal statutes in such a way as to permit the telephone prescribing of Class A narcotics under satisfactory controls and with appropriate safeguards. It was further VOTED to refer this matter of apparent conflict between Federal and State statutes to the Commissioner of Health for opinion, with a view toward informing the members of the Society as to what procedure may be followed legally and which may not.

Special Appointments To Outside Agencies

(a) *Professional Advisory Committee—Title XIX:* It was VOTED to confirm the appointment of Sidney L. Cramer, Hartford, as CSMS representative to the Professional Policy Committee, provided for in the Title XIX statutes enacted by the 1967 General Assembly (P.A. No. 548). The duty of the PAC will be to advise the State Commissioners of Welfare, Finance and Control concerning the formulation of an equitable fee schedule which will apply to doctors of medicine from October 1, 1967 until March 1, 1968, at which time it will be replaced by a "usual and customary charge" method of payment for physicians' services.

(b) *Conference Planning Committee of the Connecticut Heart Association:* It was VOTED to recommend for service with this CHA Planning Committee the following members:

William E. Swift, New Haven
Roger G. Conant, Hartford
Paul H. Twaddle, Hartford

The function of the Planning Committee is to plan and conduct a statewide conference on heart and related disease subjects as a follow-up activity to the 1964 Section National Conference on Cardiovascular Diseases. It was further VOTED to cosponsor the Conference jointly with the Connecticut Heart Association and the State Health Department, although any financial commitment associated with such sponsorship that might be requested at a later time would have to be considered as a separate item of business.

(c) *State Commission to Study Need for Epilepsy Facility:* It was VOTED to nominate John C. Moench, New Haven, and Charles G. McKendree, Greenwich, for service with a Commission to study the State's need for an epilepsy center, as provided for under Special Act No. 337 (1967 General Assembly). The statute requires that one member of the Commission be a representative of the Society, but it is possible that more than one will be asked to serve.

(d) *Drug Advisory Council—P.A. No. 555:* The "Act Revising the Laws Relating to Dependency-Producing Drugs and Treatment of Drug-Dependent Persons" calls for a Drug Advisory Council to be formed, two members of which shall be physicians nominated to the Governor for appointment who are members of the Society. It was VOTED to make nominations for these appointments as follows:

Eric E. Stietzel, Norwalk
James R. Cullen, Hazardville
Benjamin Wiesel, Hartford
Max Caplan, Meriden

(e) *Advisory Committee on Nursing Education:* P.A. No. 618 calls for the setting up of an Advisory Committee on Nursing Education, one member of which is to be a physician nominated by, and representing, the Society. It was VOTED to nominate Hilliard Spitz, New London, for appointment to this Advisory Committee.

Joint Statement On Dependent Nursing Functions

It was VOTED to approve this Joint Statement, as developed by representatives of the Connecticut Nurses' Association, the Connecticut League for Nursing, the Connecticut Hospital Association and the Connecticut State Medical Society, and to recommend to the other agencies that the document *not* be submitted to the State's Attorney General for opinion at this time. In brief, the Joint Statement reaffirms that only licensed doctors of medicine may legally practice medicine and perform medical procedures; recognizes that the "team" approach to medical care of the patient under the supervision and direction of physicians is a developing and desirable concept, and involves the participation of many other professional and technical health service providers; and fixes the responsibility on the individual physician (in his own office) and/or the medical staff (in hospitals) for assuring that all persons carrying out medical procedures under the direction of doctors of medicine are qualified to do so, either by training, experience, or both. It was further VOTED to request the President, E. Tremain Bradley, to report to the Council at the end of one year the extent to which these guidelines have been utilized, especially in hospitals (special care units, etc.), and the successes and/or shortcomings experienced by such utilization. If approved by all four agencies participating in the drafting of the Joint Statement, it is planned to distribute it widely to all concerned with a recommendation that the guidelines be followed.

Report—Chairman Of CSMS Committee On State Legislation

Isadore H. Friedberg, Newington, Chairman of the Legislative Division and of the Committee on State Legislation, joined the Council to present a comprehensive verbal report on the legislative program conducted by the Society during the 1967 session of the General Assembly. Feeling that a generally effective job had been done, in that a majority of the Society's positions had been sustained by the legislators, he pointed out several areas of planning and execution which he thinks can be improved upon before and during the next session in 1969. It was VOTED to accept Dr. Friedberg's report with thanks, and to request the Committee to develop and submit to the Council a recommended "protocol" for an on-going legislative program for the Society at state level. Hope was expressed that the requested plan would be ready for presentation at the September meeting.

New Program For (Military) Dependents Medical Care

The Council was informed that starting in the near future, a "usual, customary and reasonable charge" method of payment for physicians' services will be instituted in Connecticut by the Office of Dependents Medical Care Program. This action will be taken partly in response to the Society's request for same, and partly because of the Defense Department issuing a directive that the method be used nationwide. In the new plan, the Society will not be a formal party (as at present) to the agreement between ODMC and the fiscal intermediary, but will be expected to furnish an advisory and liaison committee and a mechanism (county medical association) for review in unresolved problem situations concerned with charges and/or utilization. It having been determined by ODMC that Connecticut Medical Service, Inc. (the present fiscal intermediary) will be unable to administer a "usual and customary charge" plan, private insurance carriers are now being approached to take over the program's administration. It is understood that the new plan will resemble Medicare B in most respects. It was VOTED to receive this report as information.

Communication—Connecticut State Society Of Anesthesiologists

Having received a communication from Sidney A. Chait, Torrington, President of the CSSA, concerning a number of matters relating to payment for anesthesia services under the Title XIX program of Medical Assistance, it was VOTED to direct the General Manager to reply to Dr. Chait's letter, emphasizing the following points:

(a) The present uniform fee schedule being used for the Title XIX program was established by the Commissioner of Finance and Control, and involved *no* "agreement" to same by the Society or its representatives.

(b) Payment for anesthesiologists' services directly to physicians is not provided for under the program as it has been operating since July 1, 1966, but such provision is, and will be, actively sought by the Society and its representatives on various advisory councils and committees to the state agencies responsible for the administration of the Title XIX program.

(c) While the legislation enacted by the 1967 General Assembly requires that a "new" uniform fee schedule be formulated and applied to physicians' services, starting October 1, 1967, a "usual and customary charge" method is to be used on and after March 1, 1968 (similar to Medicare B). Under the latter method, no fee schedule as such will be utilized. It is not anticipated that the Society's "agreement" to either of these arrangements will be sought, since they are prescribed by statute. In making nominations of "at least a majority of (twenty or more) members of the Society" to serve as a Medical Advisory Committee to the Welfare Commissioner in the administration of the "usual and customary charge" method (starting March 1, 1968), the Council plans to include representatives of all types of medical practice and it is expected that recommendations for nominees will be sought from all CSMS Sections and other specialty groups.

Further Report—Relative Values Of Extended-Care Facility Visits

Pursuant to the Council's (June 15) request that the Committee on Third Party Payments make further study of, and make additional recommendations on, the relative values of extended-care facility visits by physicians (single vs. multiple visits, routine vs. emergency visits, etc.), Howard K. Ente, Westport, Chairman of the Committee, advised the Council that the Committee planned to make a further report on these questions after it had completed its task of up-dating the Relative Value Schedule (as recently directed by the Council); that, for the present, Connecticut General be offered the guidelines contained in the Committee's previous reports; i.e., "that Connecticut General should be guided (on the subject question) by the policy that a physician's visit to a Nursing Home is equivalent in value to a House Visit," and that "under the Section of the Relative Value Study (Schedule), adopted by CSMS in 1965, which deals with home and/or nursing home visits, these matters are specifically covered (pending appropriate future updating and revising of the RVS)."

It was VOTED to thank Dr. Ente for his response to the Council's June 15 request for further study and report on this subject, and to convey to him the Council's recognition that the Committee on Third Party Payments is moving to obtain the information which is being sought for transmittal to Connecticut General re Medicare B payments for visits to patients in extended-care facilities.

Report—Ad Hoc Committee On Annual Meeting Arrangements

E. Tremain Bradley, Chairman, reported that the Ad Hoc Committee had met with the Committee on Program of the Scientific Assembly on

June 29 to discuss possible revisions in the format of the 1968 Annual Meeting of the Society, in regard to both the House of Delegates and the scientific sessions. Noting that he was the only member of the Ad Hoc Committee who was able to attend the meeting, Dr. Bradley outlined a number of tentative plans which had been developed and asked for their approval by the Council. In brief, the plans call for the House of Delegates to meet over a two-day period (instead of one day, as in the past). The opening session would be held during the forenoon of Tuesday, April 30, following which the House would recess until approximately 3:30 P.M. of Wednesday, May 1. Reference Committee hearings would be held at approximately 3:30 P.M. Tuesday afternoon, giving time for reproduction of the Committee reports for distribution to the Delegates the next day. During the hiatus between recess of the House at approximately 12:30 P.M. and the holding of Reference Committee hearings at 3:30 P.M. on Tuesday, there would be a luncheon for Delegates followed by a 90 minute program on a subject of interest to Delegates and to the general membership. On that evening, at the conclusion of the Reference Committee hearings, there would be a Delegates Dinner (similar to the one held at the 1967 meeting). It is hoped that some sections may be able to hold their annual sessions in the late afternoon of the first day (sections have previously met on the second and third days only).

On Wednesday, May 1, the Scientific Program would take up the forenoon (as in the past), and, following luncheon for registered members, resume until 3 o'clock or thereabouts. The House of Delegates would then convene for its second (final) session, with the Annual Dinner (preceded by a reception) being started at the earliest hour consistent with adjournment of the House (probably "dinner at eight") A dinner-dance (or dinner with dancing) is recommended, instead of a speaking or entertainment program. On Thursday, May 2, the Scientific Program would be continued along more or less traditional lines, concluding with the balance of the section meetings from 3:00 P.M. on. It was VOTED to approve the format for the 1968 Annual Meeting, as outlined by Dr. Bradley. Further meetings of the Ad Hoc Committee on Arrangements with the Committee on Program of the Scientific Assembly are anticipated to work out some of the details associated with implementation of the proposed revisions.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on July 26, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

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Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

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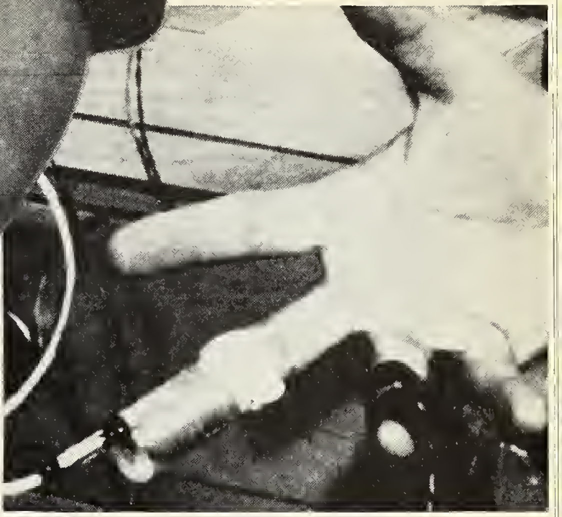

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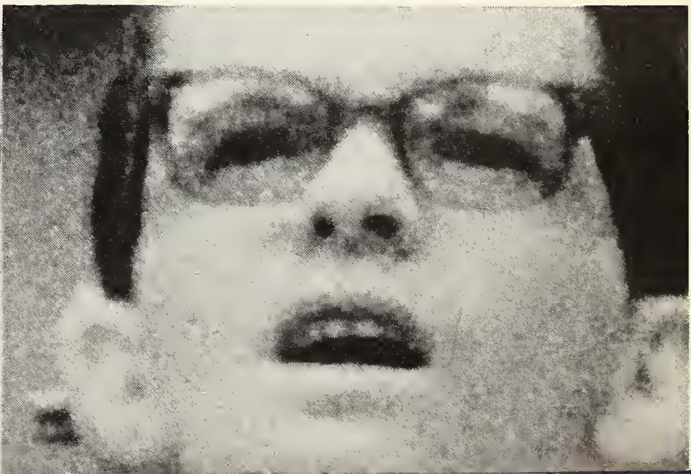

mountains, salt water, skiing, golfing, music centers, etc. Salary $18,500 per annum. Apply to Fowler White, M.D.; Acting Director; Torrington Regional Health District; 59 Field Street; Torrington, Connecticut 06790 or phone 203-482-4441.

PSYCHIATRIST—challenging position open at modern Connecticut penal institution. Opportunity to organize and develop treatment program. Salary range up to $20,500. Outstanding retirement and fringe benefits. Must have three years' residency in training center acceptable by American Board of Psychiatry and Neurology and year as staff psychiatrist; eligible for Connecticut license. Write: S. Stein, State Personnel Department, 405 State Office Building, Hartford, Connecticut 06115.

INTERNIST—to act as consultant to medical profession, hospital and nursing home administrators to assure creation and effective functioning of hospital services for participation in the Hospital Insurance Program; assists with formation of utilization review committees and reviews proposed plans of hospitals and extended care facilities; surveys institutions participating in the Health Insurance for the Aged Program and provides professional guidance to a medical staff, administrators, and owners concerning medical records, policies, and utilization review plans; evaluates medical staff organization; participates in educational programs for professional and sub-professional staff of health care facilities; prepares and studies reports. Excellent salary, good fringe benefits and retirement program. Contact: State Personnel Department, State Office Building, Hartford, Connecticut 06115 for further information.

MEDICAL DIRECTOR — Full time Medical Director for the Child Guidance Clinic for Central Connecticut, Inc. Board certification is not required. Experience with child psychiatry preferred. Regular hours, qualified staff. Progressive mental health community. Salary $18,000-$25,000, with excellent fringe benefits. Contact Mrs. B. H. Hunt, Personnel Chairman, Child Guidance Clinic for Central Connecticut, Inc., 116 Lincoln Street, Meriden, Connecticut 06450

MEDICAL DIRECTOR of manufacturing corporation in New Britain area. Internal Medicine training preferred but not necessary. Duties clinical, with nursing staff, sick room and lab facilities. $20,000 plus stock options, retirement, etc.

ASSISTANT MEDICAL DIRECTOR of insurance company division, Hartford. Internal Medicine training preferred but not necessary. Duties clinical. $18,000 plus fringe benefits.

ASSISTANT SURGICAL DIRECTOR of insurance company division. $22,500 plus fringe benefits. Some administrative experience. Duties clinical and administrative.

HOUSE PHYSICIAN—Diversified duties in accredited, voluntary hospital. Connecticut license required. Monday through Friday, every other Saturday morning. $18,000 a year. Write P. O. Box 3474, Bridgeport, Connecticut 06604.

DIRECTOR OF PSYCHIATRIC TRAINING—Board certified. To direct 3-year approved psychiatric residency program at an 1800-bed, community-oriented, geographically decentralized mental hospital. Also, to coordinate psychiatric education for nurses, psychologists, social workers and occupational therapists in university affiliated programs. Previous teaching experience necessary. Hospital affiliated with Yale University, possibility for faculty appointment. Excellent fringe benefits. Starting salary range: $18,790 to $21,710. All particulars in first letter, including references. Write: Mehadin K. Arafeh, M.D., Superintendent, Connecticut Valley Hospital, Box 351, Middletown, Connecticut.

PATHOLOGIST—full time or half-time, to direct a clinical laboratory in an 1800-bed mental hospital. Ample opportunity for research and teaching available. Well equipped and staffed laboratory. Emphasis on neuropathology. Board certified or eligible pathologist preferred. Starting salary range: $16,469 to $19,760. Excellent fringe benefits. All particulars in first letter, including references. Contact: Mehadin K. Arafeh, M.D., Superintendent, Connecticut Valley Hospital, Box 351, Middletown, Connecticut.

PSYCHIATRIST — needed for a community-oriented mental hospital. To direct or work in 300 bed comprehensive mental health center, one of several units in a 2100-bed state mental hospital. Opportunity for teaching, clinical work and research. To work with team of social workers, psychiatric residents, psychologists, occupational therapists and nursing staff. OPD, Day-care, in-patient consultation and emergency care available. Opportunity for association with Wesleyan University, Yale University and UConn. Starting salary: $15,240 to $20,000, depending on experience. Annual pay increases.

Also, other senior staff positions may be available —Salary: $2,180 to $22,700.

Excellent fringe benefits. All particulars in first letter including references. Contact: Mehadin K. Arafeh, M.D., Superintendent, Connecticut Valley Hospital, Box 351, Middletown, Connecticut.

BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Infant Nutrition. Edited by Samuel J. Fomon, M.D. W. B. Saunders Company, Philadelphia and London, 1967. 299 pp. Illustrated. $10.50.

Gout. Third Edition. Edited by John H. Talbott, M.D. Grune & Stratton, New York and London, 1967. 295 pp. $12.50

Historic Derivations of Modern Psychiatry. Edited by Iago Galdston, M.D. McGraw-Hill Book Company, New York, Toronto, Sydney and London, 1967. 241 pp. $12.50.

Manual of Preoperative and Postoperative Care. By the Committee on Pre and Postoperative Care, American College of Surgeons. Editorial Subcommittee: Henry T. Randall, M.D., Chairman; James D. Hardy, M.D. and Francis D. Moore, M.D. W. B. Saunders Company, Philadelphia and London, June 26, 1967. 506 pp. $8.50.

Bedside Medicine, 2nd Edition. Edited by I. Snapper, M.D. and Alvin I. Kahn, M.D. Grune & Stratton, New York and London, 1967. 824 pp. $18.75.

Medical Licensing in America, 1650-1965. Edited by Richard Harrison Shryock. The Johns Hopkins Press, Baltimore, Maryland, 1967. 124 pp. $5.00

Respiratory Physiology. Edited by N. Balfour Slonim, M.D., Ph.D. and John L. Chapin, Ph.D. The C. V. Mosby Company, Saint Louis, 1967. 199 pp. $8.75.

Prognosis: A Guide to the Study and Practice of Clinical Medicine. Edited by Leslie A. Osborn, M.D. Charles C. Thomas, Publisher, Springfield, Illinois, 1966. 286 pp. $10.00.

1967 Meetings

September 27—175th Semi-Annual meeting of the Hartford County Medical Association will be held at the Hartford-Hilton Hotel, Hartford. Business meeting starting at 5 P.M. and dinner at approximately 7 p.m.

October 26—Semi-Annual meeting of the New Haven County Medical Association to be held at Waverly Inn, Cheshire, Conn., beginning at 3:30 p.m.

1968 Meetings

April 30, May 1-2—176th Annual Meeting of the Connecticut Medical Society to be held at the Hartford-Hilton Hotel, Hartford, Connecticut.

PLACEMENT WANTED

SURGEON – 37 years of age, Board eligible, wishes to practice with a group or an associate in a medium-sized community.

SURGEON—Board certified, military obligations completed. Wishes to practice in a medium to small community in a solo or associate practice. Available immediately.

ANESTHESIOLOGIST – Board eligible, with residency in Internal Medicine. Wishes to practice in a small community in a solo or associate practice. Available immediately.

G.P.—49 years of age, applied for Connecticut license. Would like to practice in a large or medium-sized community in an associate or group practice.

INTERNIST—43 years of age, Board eligible. Wishes to practice with a group or an individual. Excellent training in Cardiology. Connecticut license.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

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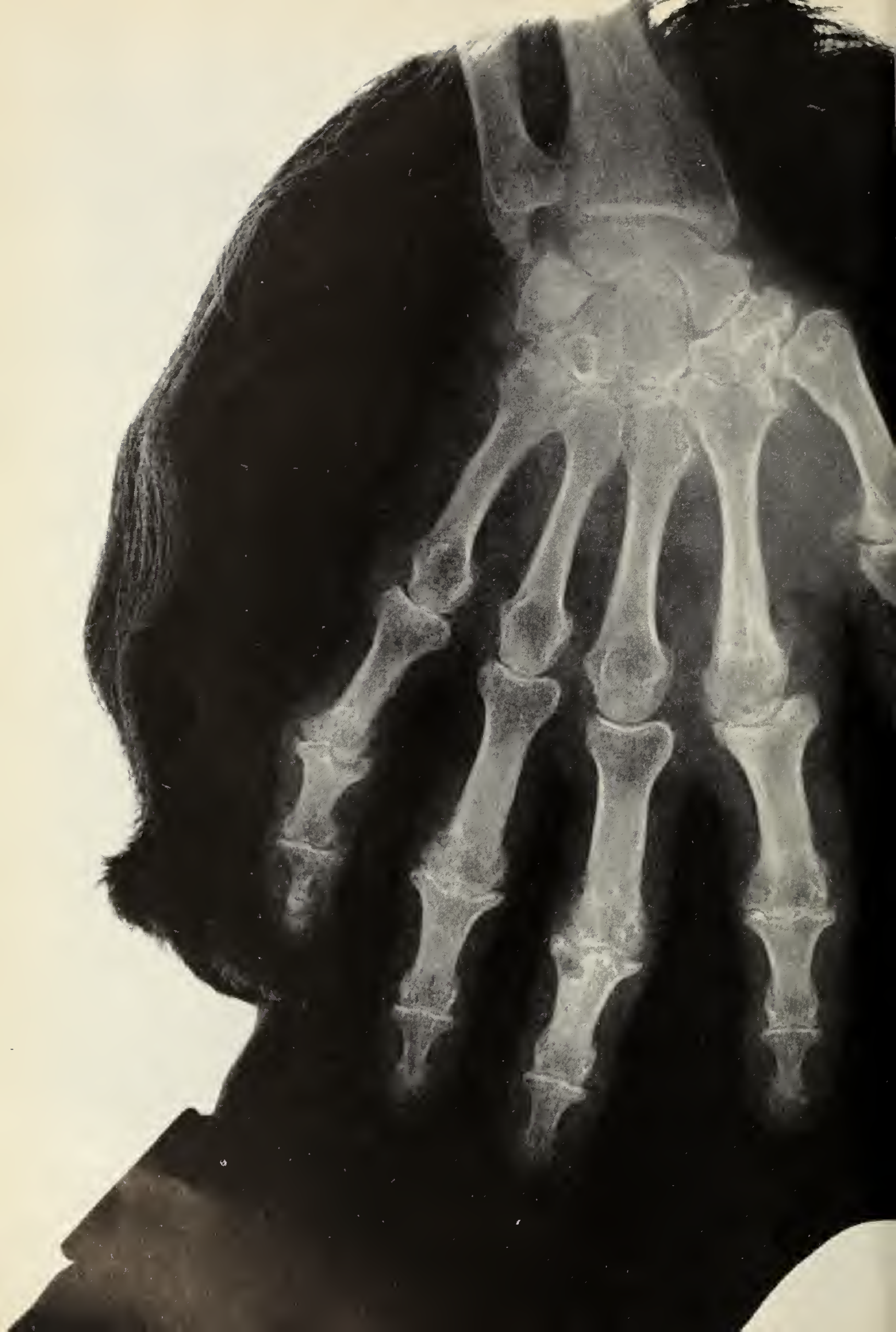

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Precautions: Keep out of reach of children. Not recommended for patients 12 years old or less. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate may result in dependence or habituation in susceptible persons—as alcoholics, ex-addicts, severe psychoneurotics. Withdraw gradually after prolonged high dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance. If drowsiness, ataxia or visual disturbances (impairment of accommodation and visual acuity) occur, reduce dose. If symptoms persist, caution patients against operating machinery or driving. After meprobamate overdose, prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and hyperventilation are reported. Give cautiously to patients with suicidal tendencies. Treat attempted suicide (has resulted in coma, shock, vasomotor and respiratory collapse and anuria) with immediate gastric lavage and appropriate supportive therapy (CNS stimulants and pressor amines as indicated).

Side Effects: Ethoheptazine and aspirin may occasionally cause nausea, vomiting, epigastric distress, and rarely dizziness. Overdosage may result in CNS depression (drowsiness and lightheadedness) or CNS stimulation and salicylate intoxication (requires induced vomiting or gastric lavage, specific parenteral electrolyte therapy for ketoacidosis and dehydration, and observation for hypoprothrombinemic hemorrhage [usually requires whole blood transfusions]). Meprobamate may cause drowsiness, ataxia and rarely allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever have been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically such as with epinephrine, antihistamine and possibly hydrocortisone. A few cases of leucopenia, usually transient, have been reported following continuous use. Rarely, cases of aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported; almost always, in the presence of known toxic agents.

Composition: 150 mg. meprobamate, 75 mg. ethoheptazine citrate and 250 mg. aspirin per tablet.

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Around The State

New Haven County

A $339,158 grant from the U.S. Children's Bureau will enable the Yale School of Medicine to join with the City of New Haven to set up a comprehensive Health Care Center for children in the Hill section of the city. The Yale-New Haven Hospital will collaborate in the program.

The announcement was made jointly by Mayor Richard C. Lee of New Haven and Dr. Fredrick C. Redlich, Dean of the Yale School of Medicine, who said that the grant is one of the first in the nation to set up such a program.

More than 8,000 children under 21 years of age living in the Hill neighborhood will be eligible for comprehensive health care—diagnosis, treatment and after-care—supplementing existing medical and dental services in that section. The new Center is expected to open about April, 1968, and the staff will provide 24-hour, seven-day medical coverage.

Dr. Charles D. Cook, Chairman of the Department of Pediatrics, has named Dr. Nelson K. Ordway, Professor of Pediatrics at the Yale School of Medicine, to be Acting Director for the new Center. He will be responsible for recruiting the Center's permanent staff and for establishing advisory committees representing medical center department, community health and welfare agencies and Hill residents.

The Hill neighborhood is defined as an irregularly triangular section in the southwestern part of New Haven, bounded for the most part by the Oak Street Connector, Legion Avenue, the West River and the New Haven Harbor. The integrated community has been selected by New Haven for consideration in Washington as the "model cities" neighborhood. The Yale-New Haven Medical Center is located in this section.

The New Center

The personnel of the new health center will include pediatricians, dentists, Child Psychiatrists, community health nurses, social workers, nutritionists, and neighboring aides. The initial staff, including administrative personnel, will number about 35. Other specialists will come to the Center on a scheduled basis or by special arrangement. Emergency care will be provided at the Center except in the case of children requiring specialized procedures, such as anesthesia, and surgical intervention. The Health Center services will be backed up by the resources of the Yale-New Haven Medical Center to which patients will be referred for selected specialty consultations and follow-up, X-rays and specialized laboratory work, emergency care not provided at the Health Center and hospitalization when indicated.

The Center, with the help of the Hill Health Council and the Redevelopment Agency, is seeking a location in a central spot in the neighborhood for quarters. Spanish speaking interpreters will be provided, both at the Health Center during operation and as necessary for personal or telephone consultation at other times.

Health services will be directed to the child as a member of the family; consequently, health workers will be brought together in "family-care teams." The health team will include neighborhood residents who will work as neighborhood aides to perform two important functions. First, under the guidance of the professional staff they will carry out certain medical and nursing tasks and offer limited counsel to families, not only in the Health Center itself but also in the children's homes. Second, they will seek out children who might use the medical and dental services and help make those services useful to them.

Nursing services will be provided by public health nurses specially assigned to the Child Health Project. These nurses will collaborate with the pediatrician, social worker, and other Health Center staff to provide comprehensive services to the children.

Screening, diagnostic, and preventive health services will be given without charge to all Hill children under 21 years of age. Treatment will be provided children from families with low incomes as defined by federal and state regulations. Children may also be eligible for treatment if: (1) the family has needs and financial obligations requiring special consideration or (2) costs of treatment are anticipated to be unusually high. All children needing emergency treatment will be treated at once without eligibility screening.

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Professional Courtesy

Adopted by the AMA Judicial Council
June 17, 1967

The custom of professional courtesy embodies the ancient tradition of fraternalism among physicians in the art which they share, and their mutual concern to apply their learining for the benefit of one another as well as their patients. The Judicial Council reaffirms and endorses the principle of professional courtesy as a noble tradition that is adaptable to the changing scene of medical practice.

Professional courtesy is not a rule of conduct that is to be enforced under threat of penalty of any kind. It is the individual responsibility of the physician to determine for himself and within his own conscience to whom and the extent to which he shall allow a discount from his usual and customary fees for the professional services he renderes, and to whom he shall render such services without charge as professional courtesy.

The following guidelines are offered as suggestions to aid physicians in resolving questions related to professional courtesy.

1. Where professional courtesy is offered by a physician but the recipient of services insists upon payment, the physician need not be embarrassed to accept a fee for his services.

2. Professional courtesy is a tradition that applies solely to the relationship that exists among physicians. If a physician or his dependents have insurance providing benefits for medical or surgical care, a physician who renders such service may accept the insurance benefits without violating the traditional ethical practice of physicians caring for the medical needs of colleagues and their dependents without charge.

3. In the situation where a physician is called upon to render services to other physicians or their immediate families with such frequency as to involve a significant proportion of his professional time, or in cases of long-term extended treatment, fees may be charged on an adjusted basis so as not to impose an unreasonable burden upon the physician rendering services.

4. Professional courtesy should always be extended without qualification to the physician in financial hardship, and members of his immediate family who are dependent upon him.

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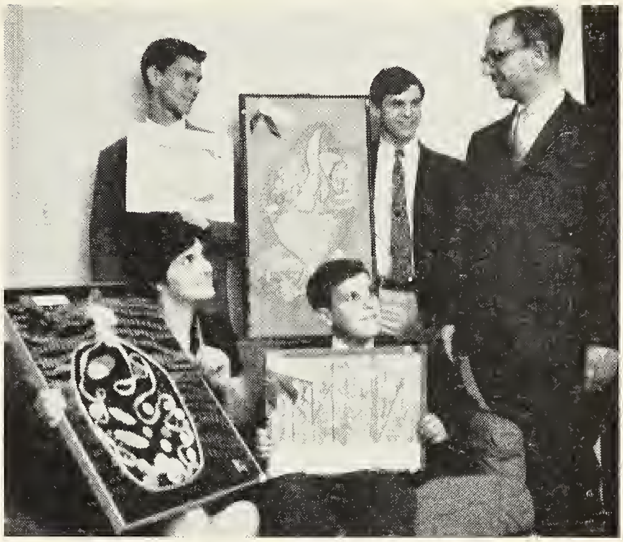
Four In Physician's Family Win Ribbons At Art Exhibit



Dr. Yale Gordon of West Hartford, who was re-elected president of the Section on General Practice of the Connecticut State Medical Society at the 175th Annual Meeting, admires the works of art his family submitted to the Connecticut Physicians Art Association exhibit at the meeting. Seated are: Mrs. Gordon whose "Pills and Frills" was awarded a blue ribbon and Barry Gordon whose "Snow Patterns" earned him a red ribbon. Standing are Justin Gordon who won an honorable mention for his "Sun-Tanning" and Harold Gordon whose "Fruit" took a blue ribbon.

CHANGES OF ADDRESS

Change of Address may be made by sending old address (as it appears on your JOURNAL envelope) and new address with zipcode number. Instructions should state whether change is temporary or permanent. Allow four weeks for changeover.

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WOMAN'S AUXILIARY TO THE CONNECTICUT STATE MEDICAL SOCIETY

Conference On Sex Education

A conference on sex education was held in New Haven in June by the Connecticut State Medical Society.

The meeting was started by some speakers stating statistics showing the need of more and better sex education in the schools. Following these given facts, these list below was suggested as a beginning.

1. Set up a bureau with local speakers.
2. Set up programs with the teachers.
3. Set up a workshop with school educators and physicians.
4. Stress health education is as important as any other subject.
5. Most pilot programs are usually successful and should be continued with some help.
6. A guide line should be set up by the Connecticut State Medical Society for organization and program.

The Connecticut State Medical Society advised a follow up meeting in the near future.

Some references given were;

A Circulum Guide in Sex Education—by Helen Manly, St. Louis, Missouri.

MMM-Health Education pamphlets and etc. as teaching aids SIECUS.

The above is one program which the counties auxiliaries might help with in getting it accepted in the schools.

This past Spring scholarships were given to the University of Connecticut to be used for students attending the special summer cours entitled "Family Living." The Ones giving these scholarships were;

Hartford County—6
Middlesex County—1
New Haven County—1
State Auxiliary—1

Another program we continue to work on is the A.M.A.E.R.F. Our State Woman's Auxiliary is procuring a set of Christmas Cards that are available this year. If any County Auxiliary is interested, they should contact the state chairman of A.M.A.E.R.F.

With Fall upon us our state board meetings are beginning this month. It is imperative that all county presidents attend these meetings. All presidents-elect are welcome, and it is suggested they attend at least one meeting before they take the office of president.

In Memoriam

Mrs. James Raglan Miller, West Hartford, Past State President; Mrs. Fritz Myer, Bridgeport, Past State President; Mrs. William Tate, Deep River.

In Memoriam

Hirata, Isao—Woodbridge; Yale Medical School, 1912. He was a practicing physician in the New Haven area for over 50 years. Dr. Hirata was a former member of the staff at the Yale-New Haven Hospital. He was a member of the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Hirata died August 11, at the age of 80.

Lovelace, Theodore R. — Waterbury; Howard University School of Medicine, 1930. Dr. Lovelace was health director of the Town of Prospect. He served as the physician of the State Athletic Commission, and as school physician for the Waterbury Board of Education. He was a member of the Waterbury Medical Association, the New Haven County Medical Association, the Connecticut State Medical Society, and the American Medical Association. He was a past president of the Family Doctors's Association. Dr. Lovelace died July 29, at the age of 62.

Woodward, Harold B. — Bristol; Johns Hopkins Medical School, 1912. Dr. Woodward was an eye, ears and throat specialist in the Bristol area for over 40 years. During World War I, he was in the U.S. Army Medical Corps and sailed with the first contingent of U.S. troops to go overseas. He was an attending surgeon at Bristol Hospital and New Haven Hospital and was made an instructor in ophthalmology and clinical assistant at the Yale Medical School. He was a member of the Bristol Medical Society, the Litchfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Woodward died August 1, at the age of 80.

Doctor's Office

Michael M. Conroy, M.D., announces the opening of an office for the practice of general surgery at 473 Broad Street, Meriden.

Thomas L. Cronan, M.D., announces the relocation of his office for the practice of general medicine to 4719 Madison Avenue, Trumbull.

Harold T. Oesau, Jr., M.D., announces the opening of an office for the practice of general surgery at 50 Ridgefield Avenue, Bridgeport.

Special Notices

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Department of Epidemiology & Public Health

Fall Lecture Series 1967

THE FEDERAL GOVERNMENT AND THE PHYSICIAN

12:45 p.m. Fitkin Theatre, Yale-New Haven Medical Center: Mondays & Fridays

18th September—Dr. Edward Cohart, Chairman & Professor of Epidemiology & Public Health, Yale University. "The Federal Government & Health: A Historical Review."

22nd September—Dr. William Kissick, Director, Public Health Programming, U.S. Public Health Service. "The Federal Government and Evolving Health Policy."

25th September—Dr. Sven Gundersen, Clinical Professor of Medicine, Dartmouth University. "What the Patient and the Physician Stand to gain."

29th September—Dr. Tremain Bradley, President, Connecticut State Medical Society. "Organized Medicine and the Patient."

2nd October—Dr. Robert Berg, Chairman & Professor of Preventive Medicine, University of Rochester. "Regional Medical Programs: The Regional Viewpoint."

6th October—Mr. John Chaffee, Governor of Rhode Island. "A Governor's view of Washington and the Physician."

9th October—Mr. Karl Yordy, Asst. Director, Regional Medical Programs, N.I.H. "Regional Medical Programs: New Relationships."

13th October—Dr. James Cavanaugh, Director, Comprehensive Health Service Planning, U.S.P.H.S. "The Federal Government, The Hospital, and the Private Physician."

16th October—Dr. Richard Weinerman, Professor of Public Health & Medicine Yale University. "Looking Into the Future: Lessons to be Learned from Other Countries"

NOTE: Titles which are underlined have been provided by the speakers, the others describe the topics to be covered.

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SPECIAL LECTURE
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"A Report on Socialized Medicine in Eastern Europe"
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This lecture is open to all who may be interested.
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NEW BOOKS IN REVIEW

ARTERIOGRAPHY: Principles and Techniques Emphasizing Its Application in Community Hospital Practice. Joseph L. Curry, M.D. and Willard J. Howland. The W. B. Saunders Co., Philadelphia and London, 1966. 328 pp. with 223 figures. $14.00.

Reviewed by: LOUIS H. NAHUM

There are now novice arteriographers and they need a safe and sane approach to this important technique of visualizing arteries. The procedures themselves are not without hazard especially in technics of coronary and cerebral arteriography where catheters can obstruct an important vessel. Nevertheless the technics can be made relatively safe when they are performed cautiously and with scrupulous attention to well established principles.

The material gathered in the book was obtained over a period of several years in a community hospital and the authors recognized the various problems encountered in over 1,200 arteriographic procedures. They clearly laid down the basic principles involved in the technique of arteriography in this book and published 223 clear unmistakable figures revealing the diagnostic value of this procedure.

There are nine chapters and an index dealing first with essential equipment and materials, technics of peripheral artery puncture, complications and precautions and finally aortography and its branches including cerebral and renal bronchial celiac and mesenteric, pancreatic and others. The last chapter deals with surgical and post mortem arteriography. Coronary arteriography is merely mentioned because as the authors point out it is highly specialized and because of the possibility of complications.

Prospective arteriographers are urged to observe arteriographic procedures in one of the large medical centers or in a community hospital where they are frequently performed first, before they begin utilizing this method in practice.

ETHICS IN MEDICAL PROGRESS: With special reference to transplantation. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., F.R.C.P., F. I. Biol. and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1966, 257 pp. $11.75.

Reviewed by: J. ALFRED FABRO

In March 1966 in London, Dr. Wolsenholme, director, assembled this conference made up of physicians, lawyers, theologians, and others concerned with the scientific, ethical, and legal problems of medical progress, especially of transplantation. Among them were the American physicians, Murray, Reemtsma, Schreiner, Strazl, and Wasmuth. Also represented were Italy, France, Holland, England, and Belgium, but not Russia.

The book is timely, stimulating and well worth reading. The medical aspects in transfusion, corneal, and organ transplantation, and intermittent hemodialysis are summarized by the physicians to give the non-physicians background from which to discuss the legal, ethical, and theological aspects.

It is fitting that the chairman was a lawyer, Lord Kilbarnon of Scotland, for eventually the law, be it statutory or judge-made, will reflect the social and theological consensus of these problems. In his opening remarks, he mentions that the common law of England and Scotland, as in many of our states, prohibits the donation of organs. A person cannot consent to a serious injury of a maiming character: i.e., giving a part of his body without some benefit to himself. Both in France and Italy living donation is prohibited.

As to prisoners, most opined that consent was not free and voluntary. (As a result of this conference the committee on transplantation of the University of Colorado has discontinued its practice of using prisoners as donors.) Except for the Americans, all agreed that minors should not be permitted to donate an organ. In Massachusetts the courts have given permission for a minor to donate an organ to a sibling, hedging the decision by saying that psychiatric testimony contended that if the court refused such permission, the donor would suffer emotionally; but he would even benefit if he were able to donate his kidney.

In order to legally tap the source of cadaver kidneys, legislation must be passed in the various countries. Lord Kilbarnon has introduced legislation in Parliament authorizing designated hospitals to remove from a dead person any organ required for medical or scientific purposes unless there is reason to believe that the deceased when alive had forbidden this to be done. The problem of legislation is more difficult in the United States because such laws must be passed by the individual states. Dr. Wasmuth, physician and lawyer from Cleveland, is pioneering in promoting such legislation. Americans are confronted by the common law doctrine of dead bodies: unless there are statutes to the contrary, a person has no power over the disposition of his dead body. The right of possession for burial purposes belongs to the next of kin. In France, doctors may perform an autopsy or remove an organ from a dead body without the consent of the family.

The problem of a definition of death took up quite a bit of discussion. All agreed that the present medical and legal definition of death is no longer adequate. Dorland's Medical Dictionary defines death: "The apparent extinction of life, as manifested by the absence of heartbeat and respiration." But there was no consensus on a definition. Alexander of Belgium and Hamburger of France wish to make death a neurological definition, to be dependent on neurological signs regardless of whether the heart is beating or not. No American present would consider a person dead if his heart were beating.

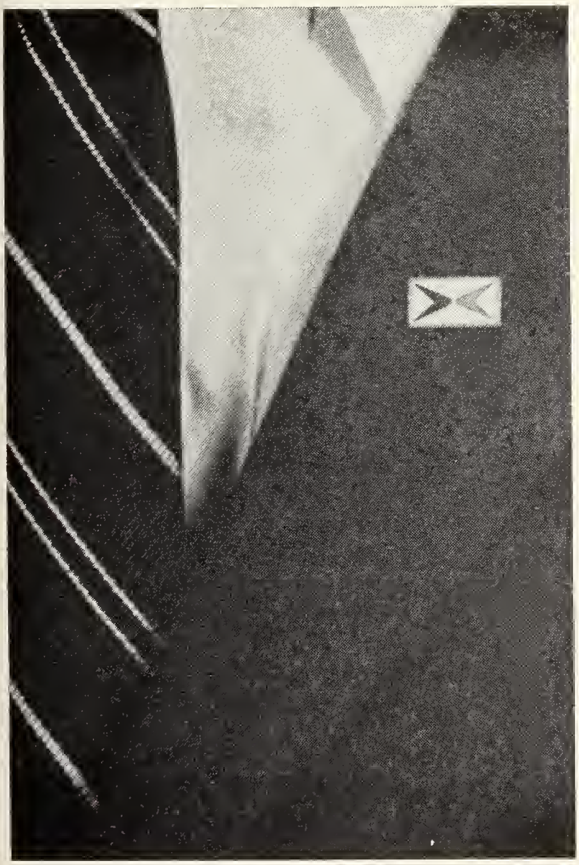
Alexander of Belgium reported nine cases in which his team removed kidneys for transplantation from patients with severe, acute brain injury whose condition was considered hopeless, but whose heart had not yet stopped beating. To establish that death is inevitable, he requires five conditions: (1) complete bilateral mydriasis (2) complete absence of reflexes, both natural and in response to profound pain (3) complete absence of spontaneous respiration, five minutes after mechanical respiration has been stopped (4) falling blood pressure, necessitating increasing amounts of vasopressive drugs (either adrenaline or Neo-synephrine) (5) a flat EEG. Revillard of Paris adds two criteria: (1) interruption of blood flow in the brain as judged by angiography, which he believes is a better sign of death than a flat EEG, and (2) of less value, the absence of reaction to atropine.

The problems of defining death were epitomized in the now famous 1963 English case of John David Potter. Potter, aged 32, was admitted to a hospital suffering severe brain injury and skull fractures received in a brawl. Fourteen hours after admission, he stopped breathing. He was put onto an artificial respirator. Physicians asked permission of his wife for one of his kidneys for transplantation. Believing him to be dead, she agreed. The next morning, a kidney was removed. The machine was then turned off. His respiration and heart then stopped. When did he die? When his respiration first stopped? Or when the respirator was turned off? The case was discussed in the press, lay and legal as well as medical, international as well as British.

The Swedes, however, were not to be outdone. Physicians there got permission from a husband to remove a kidney from his hopelessly ill and comatose wife BEFORE she was pronounced medically dead. She died about 48 hours after one of her kidneys was removed. Debate among physicians was even carried on public T.V.

Dr. DeWardener of London and Dr. Schreiner of the United States discussed the ethics and economics of hemodialysis. With demand for treatment far outstripping supply, who should be chosen? who will pay? how much money, effort, and personnel should be devoted to the problem? what hierarchy of values shall be determinant? At the present writing, a secret American committee made up of 13 medical and social scientists is studying the problem to report to the federal government on what it can and should do for such patients. Figures vary: it is estimated that from 5,000 new cases to as high as 100,000 annually could be candidates for treatment. And cost? from $5,000 to $15,000 per home dialysis a year, and from $10,000 to $25,000 per year of hospital dialysis. At present costs, some estimate that in 10 years over a half a billion dollars could be spent on this program in the U.S. annually. The report is due soon. The British Minister of Health has committed his government to the principle that everyone needing such treatment shall get it.

Medical advances have brought ethical problems that transcend the medical profession and our traditional codes of ethics. Society must be brought into the discussion as was done in this conference.



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Letters To The Editor

Packed Red Cells

To The Editor:

An overwhelming majority of blood transfusion authorities agree that 20 per cent to 40 per cent of all blood used should be transfused as packed red cells. An editorial in the *New England Journal of Medicine* (December 16, 1965, Page 1391) concludes that, "Practically the only patients who require whole blood are those who have had acute hemorrhages."

In a recent statement issued to the fifty-six Red Cross regional blood centers, Dr. T. J. Greenwalt, Director of the National Red Cross Blood Program, says:

"Whole blood transfusions increase the hazards of circulatory overload including pulmonary edema. This is probably the most common complication of blood transfusion and causes more fatalities than any other. Whole blood transfusions should therefore be avoided whenever possible.

The major purpose of most transfusions is to raise the hemoglobin concentration in order to improve oxygen transport to the tissues. Packed red blood cells are prepared by removing 225 ml of plasma-anticoagulant mixture from a unit of blood to raise the hematocrit. For this reason, the same result is achieved with a much smaller volume of packed red cells than by the transfusion of whole blood.

The proportion of packed red blood cell transfusions used in the community could well serve as an index for estimating the quality of medical practice. When the number of packed red blood cell transfusions is in excess of 20 per cent of all the blood used, then, in transfusion circles, we would consider the level of medical practice to be quite sophisticated."

For the past several years, packed red cells have been available from the Connecticut Red Cross Blood Center as a by-product of fresh frozen plasma. With the recent conversion to plastic containers for all blood collections, the Blood Center is prepared to provide unlimited quantities of packed red cells on demand. Prepared in a closed, sterile, plastic double pack, these cells have a shelf life of twenty-one days- the same as whole blood.

Aside from the clinical advantages of packed red cells, there are other significant benefits in economy and better utilization of available blood. The separated plasma will be used to prepare fresh frozen plasma and cryoprecipitated antihemophilic factor as needed, for fractionation into serum albumin, fibrinogen, and gamma globulin, and for the development of other fractions of possible clinical use.

All physicians are urged to consider the use of packed red cells in lieu of whole blood whenever possible. Not only is the patient better served in many cases, but clinically valuable blood components and fractions are thereby made available, and better utilization of scarce blood supplies is realized.

J. C. Early, m.d.
Director
Connecticut Red Cross Blood Program

100 Farmington Avenue
Hartford, Connecticut 06105

To The Editor:

In the past decade and a half, longer acting nitrates such as pentaerythritol tetranitrate (PETN) have become available to reduce the incidence and severity of attacks of angina pectoris. PETN has recently been made available in a variety of sustained release forms containing amounts of active ingredient ranging from 30 mg. to 80 mg. While patients vary in their need for PETN this seems like a rather wide dose range and a logical query seemed whether 80 mg. in a sustained release form had any real advantage over a preparation containing less PETN and whether there might be any appreciable difference in the incidence of side effects.

A group of 50 patients with symptoms of angina pectoris were assigned in a random manner to twice a day treatment with either a sustained release preparation consisting of a capsule containing 45 mg of PETN (Duotrate-45®) or a tablet containing 80 mg. of PETN. These were dispensed in opaque bottles so that the administered drug was not known to me.

At each weekly visit for a month, an estimate was made of any change in nitroglycerin intake or exercise tolerance. Side effects were noted. It was found that 80 per cent of the cases treated with the 45 mg preparation were felt to have had excellent to good results, and 68 per cent of those treated with the 80 mg. tablet had a similar improvement. These results are about equivalent. The difference in the side effect, headache, was striking. Only one of 25 receiving the 45 mg. dosage form complained of headache, whereas 9 of 25 receiving the 80 mg. preparation had this complaint.

It would seem from these observations that dosage levels as high as 80 mg. of sustained action PETN preparations have little advantage over 45 mg. in the prevention or amelioration of angina attacks in most patients, and that the use of the high dose is accompanied by an increased incidence of side effects, and hence less patient acceptance.

Ralph E. Cole, m.d.

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AMA Journal Evaluates Contraceptive Methods

"The population explosion and the frightening magnitude and complexity of the problems it is creating continue to be of worldwide concern," says an editorial in the Journal of the American Medical Association.

Within little more than a decade, the editorial notes, two highly effective methods of conception control have been developed: oral contraceptives, and more recently, intrauterine contraceptive devices (IUDs).

Both types of conception control are evaluated in this issue of The Journal in statements by the AMA Committee on Human Reproduction and the AMA Council on Drugs.

"Because of their convenience and proven effectiveness, the oral contraceptives have been widely accepted by both physicians and patients, and it is estimated that approximately seven million women (five million in the United States) are now using them," the editorial said.

"However, it has also been recognized that much information is lacking about the actions of these preparations."

Study groups operating under auspices of the World Health Organization and the U. S. Food and Drug Administration have published reports that present a balanced opinion on oral contraceptives, the editorial said.

Opinions differ on the oral contraceptives' relationship to cancer, liver function changes, and circulatory disease, the editorial notes.

"These sharp differences of opinion should be welcomed, since they help to stimulate further research directed toward obtaining answers to these problems," the editorial said. "In the meantime, an uneasy responsibility rests with the practicing physician who must properly guide his patients in the use of these preparations without engendering undue alarm, and yet be alert to the possibility that some unusual response may signal a serious adverse reaction.

In contrast to the oral contraceptives which prevent pregnancy by a complex hormonal action, the action of the IUDs seems to be a simple mechanical phenomenon (althought much information is lacking about how IUDs actually work). Side effects of the IUDs are generally due to the problems posed by placing a foreign body in the uterus.

"The IUDs and the oral contraceptives represent another of man's successful efforts toward intelligent control of his environment," the editorial said. "Undoubtedly these methods presage the development of even better methods of fertility control.

"In the meantime, to extend their usefulness, convenience, and safety, more clinical investigations . . . are needed to resolve the major problems that exist. Any delay should be avoided, and the physician should be repeatedly urged to report the nature of all adverse reactions he might see."

Surgeon Describes Value Of Ultraviolet Light In Early Detection Of Pseudomonas In Burns

A diagnostic tool borrowed from the dermatologist is helping a Miami surgeon discover a deadly form of burn infection in its earliest stages.

The long-wave ultraviolet light from a Wood's lamp causes a characteristic green glow wherever colonies of Pseudomonas aeruginosa bacteria are growing on the skin, according to C. Gillion Ward, M.D., University of Miami, Miami, Fla.

Dr. Ward reported his detection method here at a scientific session of the 116th Annual Convention of the American Medical Association.

Quick detection of Pseudomonas infections is imperative in burn cases.

Pseudomanas grows in the intestinal tract and on the skin among other places, and quickly invades injured tissue. In burn victims, whose resistance to infection is seriously reduced, any infection can be critical but a Pseudomonas infection is especially feared by physicians because the Pseudomonas organism is resistant to most antibiotics.

Detection, said Dr. Ward, has previously been accomplished by:

(1) the time-consuming method of growing bacteria from the wound in the laboratory.

2) observing in the wound the visible blue-green pigment pyocyanin which is elaborated by some but not all forms of Pseudomonas. Visible amounts of the pigment may not become apparent until the infection is well established.

In either method of detection, he pointed out, by the time a diagnosis is certain the infection may be overwhelming.

The alternative method described by Dr. Ward is based upon the fact that all pathogenic forms of Pseudomonas produce a second pigment, fluorescein, which is not visible to the unaided eye but fluoresces strongly under ultraviolet light.

Even wounds which appear clean may be seen to fluoresce when examined by Wood's lamp, Dr. Ward said.

Dermatologists use the Wood's lamp regularly to examine the skin for organisms, including Pseudomonas.

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References: 1. Batterman, R. C., and Grossman, A. J.: Fed. Proc. *14*:316, 1955. 2. Goodman, L. S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Company, 1965, p. 331. 3. Roth, J. L. A., *et al.*: Gastroenterology *44*:146, 1963. 4. Conney, A. H., and Burns, J. J.: J. Pharmacol. Exp. Ther. *128*:340, 1960. 5. Settel, E.: Clin. Med. *6*:1373, 1959. 6. Berman, H. H., *et al.*: Dis. Nerv. Syst. *25*:430, 1964. 7. Darienzo, C.: Ibid., *27*:189, 1966.

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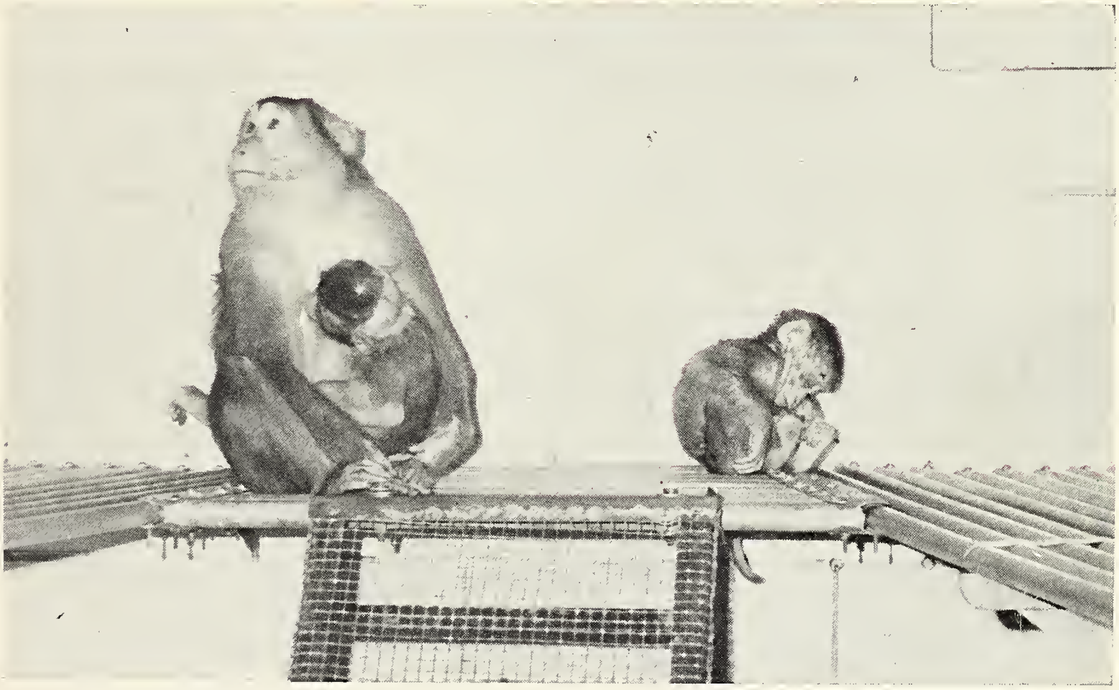

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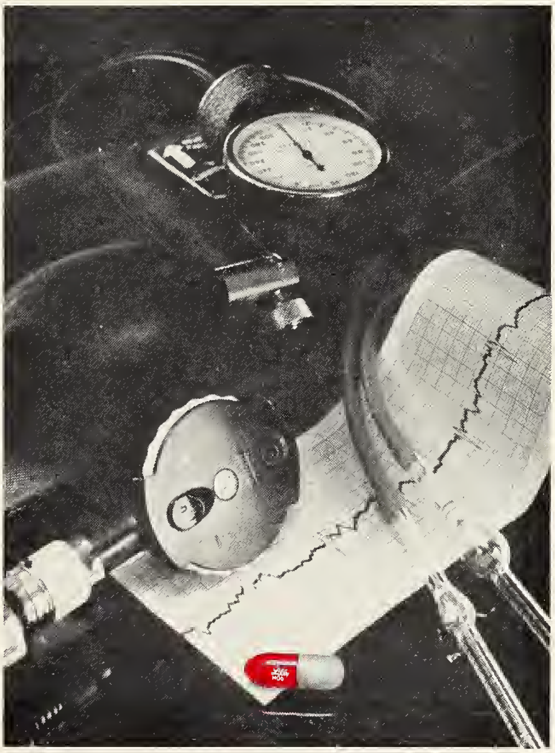

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editorials

Dextran And Isoproterenol In Shock

Cohn et al[1] suggest dividing patients in shock into two categories. One designated as "vasoconstricted", exhibit cool moist skin, thready pulses, and another nonvasoconstricted have warm skin and full pulses as well as hypotension. In the vasoconstricted the total blood volume was lowest being 55 ml./kg. In the nonvasoconstricted the total blood volume was not so low being 63 ml./kg. An attempt to correct the hypotension and shock in twenty-three nonhemorrhagic type patients with rapid infusion of 500 ml. of ten per cent Dextran 40 revealed unusual and gratifying results.

Dextran 40 is a polysaccharide which acts as a plasma expander and also has a direct rheological effect in inhibiting red cell sludging and improving blood flow. The patients with nonhemorrhagic shock apparently responsed much better after rapid infusion with Dextran 40 in restoring cardiac output than can be accomplished by vasopressor drugs. In the shock patients mean arterial pressure was raised and pulse pressure increased, heart rate slowed, cardiac output increased and the stroke volume increased from 31 to 56 ml. This meant that Dextran 40 infusion released the peripheral vasoconstriction in shock, increased the venous return and the stroke volume. The clinical course was gratifying in sixteen of the twenty-three shock patients designated as vasoconstrictive. They showed obvious improvement, the pulses became fuller, the cool skin warmed up, the sweating ceased, the patients became more alert and urine flow increased. Ten of the sixteen patients required but one 500 ml. injection but in six it had to be repeated.

No toxic effects of Dextran 40 was noticed. The volume expansion produced no pulmonary congestion even in the patients who also had heart failure. No bleeding phenomena and no allergic reactions were encountered although in one patient who received several infusions of dextran, eosinophilia was noted two weeks later.

The nonvasoconstricted shock group also exhibited a significant increase in cardiac output after Dextran. Before administration these patients had a lower central venous volume, slower heart rates and were usually normovolemic. In this group, there was a high incidence of alcoholism, cirrhosis, emphysema and malignancy. Many of the nonvasoconstricted patients remained hypotensive after the cardiac output was restored to normal by means of dextran and this treatment clearly unmasked the existence of a functional impairment of the heart. Whether or not cardiac deterioration is truly a factor in shock, it is self-evident that impairment of cardiac contractility can adversely affect the prognosis in shock since seven of Cohn's patients in this category died despite treatment.

The low molecular weight dextran commends it as the treatment of choice in all types of hypotension and shock associated with low or normal central venous pressure. The low molecular weight preparation has several theoretical advantages over clinical dextran in the treatment of nonhemorrhagic shock. It has a higher concentration (ten per cent) and this results in greater acute volume expansion by the mobilization of extra vascular fluid and its more rapid disappearance from the circulation minimizes the possible dangers of over expansion. The lower molecular weight particles also appear to have other rheological properties and tend to produce coagulation defects less often.

THE COVER

THE INFANT is completely disengaged from the mother (not his) and her infant sitting nearby in close ventral-ventral contact.

The photograph is reprinted by permission of I. Charles Kaufman, M.D. and Leonard A. Rosenblum, Ph.D., Primate Behavior Laboratory, Department of Psychiatry, Downstate Medical Center, S.U.N.Y., Brooklyn.

In addition to their paper in *Science,* a longer paper, entitled, "The Reaction to Separation in Infant Monkeys: Anaclitic Depression and Conversation-Withdrawal," by I. Charles Kaufman, M.D. and Leonard A. Rosenblum, Ph.D. has been written for *Psychosomatic Medicine.*

The deleterious circulatory effects of prolonged vasoconstriction are well known.[2] It causes tissue hypoxia, intra-vascular pooling, a loss of plasma volume which aggravates deficiency of venous return. The vasoconstrictive effects are the result of reflex mobilization of the sympathetic nervous system to guard blood flow to the brain and to the heart. Numerous pharmacologic agents have been recommended to combat it including adrenergic blockers, ganglionic blockers, vasodilators, corticosteroids and isoproterenol. Now that dextran can reduce the peripheral vascular resistance in all patients, restoring it to the normal range, the problem arises whether we can improve our results in those shock patients in which myocardial inadequacy contributes to the severity of the shock state.

Carey[3] pointed out that there is a diminished function of the left ventricle in an anesthetized dog after hemorrhage and that proper perfusion of the coronary arteries of these animals did not seem to save their lives. There is however little doubt that cardiac function is decreased during some shock states and that heart failure contributes to mortality after prolonged and severe oligemia. As in Cohn's series, Carey reports twenty-three patients of whom seven did not respond with increase in cardiac output after dextran. In such patients the Starling mechanism has obviously been stretched to its limit and existing tachycardia indicated an excessive use of the sympathetic mechanism to improve the contractile power of the heart.

All Carey's patients who failed to respond to volume loading with dextran did show marked response to isoproterenol. This catecholamine dilates vessels in the peripheral circulation and at the sane time has a potent inotropic effect on the heart muscle. Part of the favorable response of these patients might also be due to reducing the pulmonary vascular resistance thereby facilitating transfer of blood from right to left heart chambers.

We thus have evidence that plasma expansion is advisable in all patients with shock while catecholamine infusion may be necessary in those patients who fail to respond to plasma expansion alone. Since hemodynamic function in patients improved after volume loading we have evidence that peripheral circulation failure is an important parameter in the shock patient. However our aim is restoration of cardiovascular function and complete recovery. We must therefore be prepared not merely to expand volume, reduce peripheral vascular resistance, but when needed also to improve myocardial contractility. Clearly we now have procedures available for both.

L.H.N.

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Heparin In Thrombotic Microangiopathy

Purpura fulminans is a term applied to severe and usually fatal disseminated intravascular thrombosis with extensive infarction and tissue necrosis occurring during or immediately following acute infections such as scarlet fever or meningococcemia. As Antley and McMillan[1] showed in their recent successful treatment of a three and one-half year old child the syndrome resulted from depletion of blood coagulation factors. Their study has pointed the way to recognition of this hitherto fatal complication by simple laboratory tests and a rationale for successful therapy by intravenous heparin.

This most devastating example of a syndrone that can result from a wide variety of causes has pathologic features resembling the Schwartzman phenomenon in rabbits in which the reaction is characterized by acute consumption of clotting factors and intravascular deposition of fibrin leading to ischemic necrosis. It is exactly as if the plasma constituants involved in clotting have precipitated out and the blood contains only serum minus fibrinogen, platelets, prothrombin and certain other factors required for clotting. As a result the blood is now incoagulable, the microcirculation is blocked by widespread thrombi and bleeding occurs.

The initiation of events of intravascular clotting is not yet understood. There are, however, a large number of human diseases leading to this syndrone of intravascular activation of the clotting system and a resulting acute depletion of some of the clotting factors.[2] The mortality is very high when typical coagulation defects exist. In hospitals where complete coagulation studies are not possible minimum studies should include assessment of platelets, determination of plasma prothrombin, partial thromboplastin and thrombin clotting times for these tests will reveal that coagulation factors have been used up and therefore a rationale for therapy.

To prevent further precipitation of thrombi in the microvasculature, heparin has been recommended[3] and was successful in Antley and McMillan's case. Twenty-four hours after anticoagulation with heparin was started recuperation of the coagulation system began and with it improvement in the patient. There has been already extensive experience with heparin in this type of intravascular thrombosis.[4] Antley and McMillan administered 1 mg. per kg. of body weight every four hours intravenously until the coagulation functions and platelet counts became stabilized at normal levels. The findings suggest that premature discontinuance of heparin is contra-indicated because of the danger of relapse.

An understanding of the pathophysiology of this type of "consumption—coagulopathies" lends a theoretical support to the use of heparin although it is understandable why a physician who attends a bleeding patient might hesitate to use anticoagulants. However, laboratory tests necessary for the proper diagnosis are not exceptionally difficult and are available in any community hospital. Once the diagnosis is established, the bothersome question might be why not replace the precipitated coagulation factors? Replacement therapy with blood may, of course, be required to combat shock and anemia.

There is, however, always the danger that if we replace the depleted clotting factors, this will result only in increasing the clottable substrate and worsen the clinical picture. It is, therefore, not surprising that caution has been recommended in the treatment of "hypofibrinogenemias" with fibrinogen. Indeed fibrinogen has aggravated the course of purpura fulminans. If we recognize that the administered fibrinogen at once adds to the amount of already existing intravascular clot, it becomes clear that what is necessary is to prevent fibrinogen conversion to fibrin and this as noted is best accomplished by heparin.

The use of steriods seems less well defined in this group of diseases. Dexamethasone did not seem to inhibit the evolution of purpura fulminans in Antley and McMillan's case. On the basis of experimental data steroids would appear to be contra-indicated especially in septic cases and those in which endotoxin is involved. Since we already know that heparin is life-saving in this condition, such suggestions as hyperbaric oxygen and dextran which have been reported to be useful in the treatment of purpura fulminans can well be left to researchers until their value can be better defined.

Finally, there remains a word to be said about the role of fibrinolysis. On theoretical grounds therapeutic measures to enhance fibrinolysis in a late stage of the disease when the circulation is widely obstructed by thrombi might prove beneficial. However, the value of such agents that promote fibrinolysis is not as yet will defined and there is as yet no evidence that these agents are able to augment the results that can be achieved by heparin alone.

We must remember that necrotic lesions resembling purpura fulminans are seen in other conditions that do not result from intravascular clotting. This is why "consumption—coagulopathy" must be carefully substantiated before heparin is given. We already have evidence of failures as well as successes with heparin in treatment of thrombotic thrombocytogenic purpura and it is also important to learn of possible failures in purpura fulminans treated with heparin to gain more insight into this problem.

L.H.N.

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Average Remaining Lifetime At Birth

Longevity which is measured as the average remaining lifetime at birth has increased markedly in this country in each decade from 1900, when it was 46.3 years for males and 48.3 years for females, to 1964 when it was 66.9 years for males and 73.7 years for females. However, a glance at the tables further reveals that there has been very little increase since 1954 when the average remaining life at birth was 66.7 for males and 72.7 for females. Furthermore, other countries are still increasing their averages for both sexes so that the United States has fallen from 14th place among the nations of the world for males in 1949 to 31st place in 1964.[1,2] For females it has fallen from 9th to 11th place in this interval of time. The five leading countries are Netherlands, Sweden, Norway, Israel and Denmark.[3]

In the meanwhile the cost for health services in this country has risen from twelve billion in 1949 to forty-four billion in 1964[4,5] Allowing for increase in population, and decrease in the value of the dollar, there still remains a great discrepancy between what we received for our money in 1954

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and what we are receiving today from the marked increase in expenditures without any real increase in longevity. However, during this time other countries have continued to improve their longevity without as great a demand on the gross national product.[3]

Two questions arise essentially of a medical nature when viewing this sudden cessation of progress after several decades of increase. Has there been a sudden curtailment of money and effort put into medicine and health programs to account for the cessation of progress? Is it peculiar to this country or is the trend world-wide? As seen above, we have not curtailed the money put into health but have markedly increased it without significantly increasing longevity for males since 1954 and with only a slight increase for females. Furthermore, it is not a worldwide trend.

The statistics for the U.S. include figures for both white and colored populations, and as is well known the difference in the medical care available to the two groups has been, and to a considerable extent, shockingly great. In 1900, the difference in longevity of the two groups was about fourteen years. Now it is about six years, still a great difference. Thus, if the organization and distribution of medical services in this country were so improved as to bring the lowest 12 per cent up to the level of the highest 88 per cent, it would require a considerable increase in expenditure over the forty-four billion spent in 1964.[3]

There is no doubt that in countries in which infectious diseases are one of the largest causes of death, medicine, both in its preventive and therapeutic activities has been, is and will continue to be the most important single determinant of longevity. However, in countries in which degenerative diseases greatly predominate over infectious ones as causes of death and the level of care is moderately high, this is no longer true. Even huge amounts of money and effort put into medicine can have only nominal effects on average remaining lifetime at birth. The controlling factors must lie elsewhere than in medicine. Obviously the successful attack on the medical determinants of longevity have worked so well that the remaining factors are largely non-medical at present, unless or until we learn how to prevent or cure cancer, heart disease, strokes and the degenerative diseases. What are some of the non-medical ones.

Automobile accidents in 1964 accounted for 2.6 per cent of all deaths up from 2.2 in 1949. We know that the outcome of a given accident may be influenced by quality of ambulance services and accident room techniques, but the chances of reducing significantly the 2.6 per cent by increased medical efforts are small. The controlling factors are the design of the roadways, the design of the cars and above all the prevalent social attitudes about speed, about care and courtesy on the roads, and about drinking before driving.[6] Since the relative ineffectiveness of medicine is already recognized, the problem obviously must be attacked by modification of roadways and cars. It is the human attitude here at all levels which has produced a reluctance to attack vigorously this serious problem.

Another non-medical one is smoking, especially cigarette smoking. Cancer of the lung accounted for 2.54 per cent of all deaths in this country in 1964 up from 1.35 per cent in 1949. This is not a medical problem although it is thought of as such. There has been definite improvement in lung surgery, radiologic detection and treatment of cancer during a time when the death rate from lung cancer has doubled. Smoking is primarily responsible for this disease and contributes heavily to lung disease, heart disease and reduced longevity.[7] Nevertheless doctors have had little success in diminishing smoking in the population, in their patients and not too great a success even in themselves. In 1966 the sale of cigarettes in this country reached an all time high. Obviously the attack on smoking and its effect on lung cancer and longevity in general lies through sociology rather than through medicine. Medical efforts are still multiplying but the attack on smoking is lagging.

It is possible that improvement in our average remaining lifetime is more likely to result from the study and control of factors not commonly thought of as medical, over urbanization, television, the automobile, diet, interpersonal relations as influenced by crowding, by industry. These general factors have specific components such as industrial hazards, air pollution, detergents and other chemicals in water. However, vitamins and insecticides in the food are coming under scrutiny and being subjected to analysis. How much we can blame these vaguely recognized ills on these specific items we don't know, but they are common to other industrialized countries whose life expectancy is ahead of ours and they do not explain the descrepancy in the life expectancy between males and females.

One is driven back for possible explanations to more subtle factors in the human environment, little understood and often not even suspected. Dubos[8] has well presented the complexity of the processes and factors that are involved in the ecology of man and his diseases. We need to know more about the role of physical exercise both among males and females in its effect on life-span.

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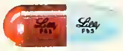

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success. There is no reason to believe that man is an exception to the general rule that mammals have a life-span that is characteristic of their species. In the Holy Bible we find stated that man's normal span is seventy years or a little more[9] and current figures give no reason to think that it has or will soon change very much. We are now approaching a plateau[3] as the recent figures from the Netherlands and Israel and the Scandinavian countries show and that we may expect the average remaining life-span at birth to remain in the low seventies and perhaps a little longer in some.

L.H.N.

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Dealing With One Of The Major Diseases Of Civilization: Obesity

If we make a search of the literature of the past one hundred years about obesity we find that it has always been clear that sugar and starch were found to be the greatest offenders that corpulent persons give up their overeating with the greatest of difficulty, that exercise was always considered one of the most effective and agreeable methods of reducing corpulence and that obesity was an evil "that dreadful tormenting parasite on health and comfort."[1] But since these things about obesity have been known for a long time and the condition remains with us fully as prevalent as of old it must be clear that the problem is complicated as well as simple.

It is simple because the treatment requires nothing more than an induction of a negative caloric balance and there is now much information as to how this can be brought about. It is complicated first because we are still ignorant of the precise physiological factors that determine caloric balance and second because we still fall short of knowing how best to persuade our patients to follow the instructions that we know will constitute effective treatment.

Our ignorance of the physiologic factors involved in obesity does not in fact greatly affect our approach to therapy except in myxedema. Some people put on excessive weight and it is the physicians task to treat them. In the normal person the amount he eats is determined by his body's caloric needs. His hunger and his appetite satisfy only his caloric requirements. The obese person satisfies his hunger and goes on to eat food he likes long after he has satisfied his caloric needs. He now finds it is his taste for palatable foods that increase his caloric intake, especially if it is a substitution for emotional difficulties. Often these are sufficiently mild to be amenable to simple explanations and sympathetic support. Occasionally unless extensive psychotherapy is possible we must accept that obesity is at least in some degree inevitable.

The caloric output depends upon the basal metabolic rate and the calories needed for activity, remembering also that metabolism rises in a particularly cold environment to preserve body temperature. The amount of calories required for physical activity is a relatively small part of total caloric requirements however. In order to increase caloric output by 300 calories, less than 10 per cent of average daily intake, we would need to walk two hours or swim vigorously for one half hour or bicycle for one hour. Although some people say that it is hardly worth while to recommend exercise for this reason, the fact is that activity is somehow needed in order that the appetite center can perform its normal automatic adjustment of appetite to caloric expenditure. The effect of activity then is to improve the balance between input and output of calories not only by the calories used up by the work itself but also by the calories given off simply as heat.

Since obesity can only come about by an intake of calories that is greater than the output of calories, its treatment lies in reversing this by reducing intake of calories or increasing output of calories or both. Generally this is not difficult. The trick is for the patient to maintain his equilibrium at a lower weight so that obesity does not reoccur.

If we look at the protein fat and carbohydrate of a diet, it is easy to see that reducing protein from daily intake of 100 grams would hardly yield a significant caloric deficit without endangering the health of the individual. A reduction of fat to produce a daily caloric deficit of 500 calories would for most people lead to an unpalatable diet that they would find difficult to maintain. The reduction of carbohydrates on the other hand can lead to a considerable reduction in calories and give a diet that is still very acceptable. In practice this kind of a diet would require no weighing, calculating or measuring other than the avoidance of carbohydrate rich foods. On such a diet the proteins and fats will be found to regulate themselves at levels that are no higher than in the ordinary diet. In fact one can ask his patient to eat as much as he likes of foods that contain little or no carbohydrates such as meat, fish, eggs, cheese, green vegetables, butter, cream and one glass of milk if the carbohydrates are kept to about 50 grams. The result will be a diet in which calories are automatically restricted and the patient need never feel hungry.

Such a diet can be recommended on many other grounds. It is sound nutritionally. The foods that are being restricted are mostly those that are rich in "empty " calories. The diet is one that is easy to get used to, so it achieves the permanence of weight loss, that is so rare when other dietary regimes are followed. It is socially highly acceptable, for the patient can eat with the family or at social gatherings all the foods with the exception of those that are rich in carbohydrates. Last but not least is the probable link between arterioslerosis and a high consumption of sugar, an additional reason for reducing what is for many people a major source of daily calories.

We saw earlier that it is also possible to affect the other side of the equation—the disposal of calories by making certain that one is undertaking a moderate amount of physical activity, walk more, work more and avoid the latest labor saving devices. Unfortunately patients tend to accept the change to a more active way of life even less readily than the need to change to a different sort of diet. In these circumstances we may have to be content with less than optimal weight loss although the low carbohydrate can achieve considerable results.

If the patient tells us that such a regime is not possible or not practicable or not effective one can be pretty confident that the patient has insufficient incentive to lose weight. The patients may not reveal their lack of incentive so directly but merely say "I will try" instead of "I will do it." We all know, however, it can be done with sufficient motivation. A person whose livelihood depends on the avoidance of overweight can certainly remain slim as witness the dancer, or the jockey. Without doubt we often do not know how to discover or create the right incentive but we would do well at least to recognize the overriding necessity to do so.

Admittedly there remain many problems to solve in the inter-relationship between acquisition and disposal of calories or how we actually preserve our caloric balance. But this does not mean that treatment cannot be effective. It can, if the patient is adequately motivated to lose weight, for we now know ways in which this can be done relatively painlessly. The most important single factor in reduction of overweight is the restriction of dietary carbohydrate. If in addition we can make our patients even only a little more active, we shall be going a long way in dealing with one of the major diseases of civilization.

L.H.N.

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Emotional Deprivation And Stunted Growth

In Kaufman and Rosenbloom's graphic description of the depressed behavior of infant monkeys separated from their mothers, there are hints of loss of appetite, poor feeding and other disturbed somatic functions as a consequence of psychic trauma. We have also known that there are endocrine discharges mediated through the higher centers of the nervous system as a part of normal neuroendocrine regulation. The classic example is the startling response with sudden liberation of norepinephrine and epinephrine and their influences on heart rate, peripheral vasoconstriction, contraction of pilomotor muscles, palmar sweating, suppression of insulin secretion, glycogenolysis. Water diuresis is interrupted, there is increased ACTH secretion, contraction of spleen with enrichment of the circulation with red cells. There may even be increased fibrinolytic activity, all calculated to improve the ability to fight or take flight. These are adaptive mechanisms eloquently stated by Walter Cannon.[1]

There are also disturbed endocrine phenomena which are associated with psychic pressures. One is hyperthyroidism which has often been noted to follow some emotional trauma. Pseudocyesis is seen in young women with an intense desire for pregnancy. Temporary amenorrhea, encountered among teen-age girls who are struggling to adjust

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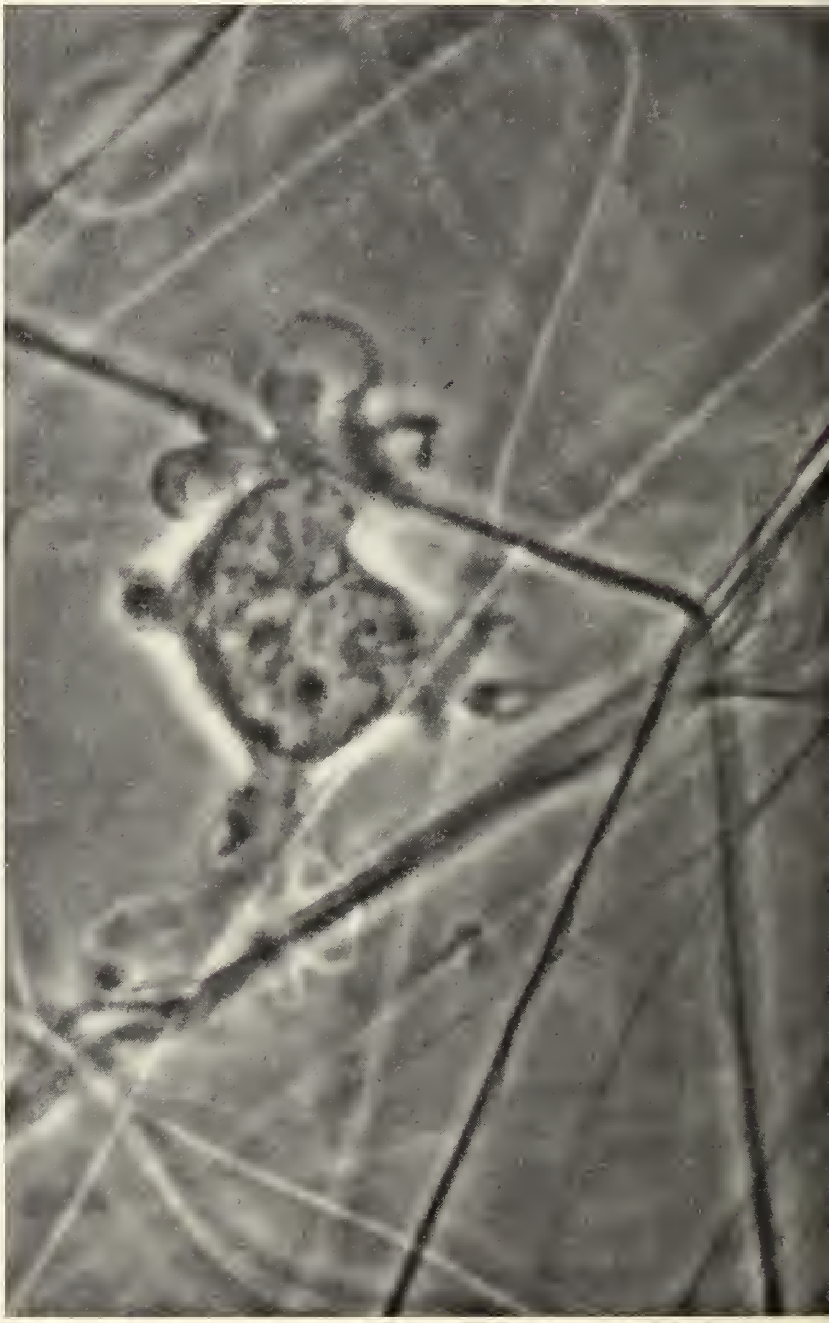

Worldwide clinical experience confirms the predictable therapeutic potential of Synalar

It is particularly gratifying that the promise of the advanced chemical design and high order of bioassay activity of Synalar (fluocinolone acetonide) has been confirmed by widespread therapeutic application. Indeed, the impressive clinical response rate of Synalar has been documented in no fewer than 232 papers from 22 countries.

Representative Clinical Results with Synalar*

Efficacy Documented in over 4,000 Patients

Condition	Number of Publications	Number of Patients	Significant Improvement†
Contact Dermatitis	27	750	713
Eczematous Dermatitis	21	472	409
Seborrheic Dermatitis	18	442	426
Atopic Dermatitis	24	460	426
Psoriasis	36	1,699	1,510
Neurodermatitis	18	351	324
Total	144	4,174	3,808

*Complete bibliography on request.

†Expressed by the authors as excellent, very good, good, complete remission of inflammation, etc.

Prescribing Information

For initiation of therapy: Cream 0.025%, 5 and 15 Gm. tubes, 425 Gm. jars; *for emollient effect:* Ointment 0.025%, 15 Gm. tubes; *for maintenance therapy:* Cream 0.01%, 15 and 45 Gm. tubes, 120 Gm. jars; *for intertriginous or hairy sites:* Solution 0.01%, 20 cc. and 60 cc. plastic squeeze bottles; *for infected inflammatory dermatoses:* Neo-Synalar® Cream (0.025% fluocinolone acetonide, neomycin sulfate, equivalent to 0.35% neomycin base), 5 and 15 Gm. tubes.

Contraindications: Tuberculous, fungal, and most viral lesions of the skin, (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. **Precautions:** Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. Prolonged use of any antibiotic may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy should be instituted. When severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. **Side Effects:** Side effects are not ordinarily encountered with topically applied corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. The neomycin in Neo-Synalar Cream rarely produces allergic reactions.

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to a life away from home, is certainly an example of psychic influences disturbing normal endocrine functions.

The influence of emotional influences upon secretion of the growth hormone is now emphasized again by Powell and his associates[3,4] in a study of thirteen children who failed to grow because of an abnormal home environment leading to severe emotional disturbances. The association of growth retardation with emotional deprivation was already noted by Talbot et al in 1963[5] who suggested that functional suppression of growth hormone secretion was responsible for growth failure. Experimental support was already at hand for this speculation from experimental studies that psychologic factors could destroy appetite and lead to inadequate calorie intake and malnutrition.

Powell's studies, however, indicated that in all likelihood the growth failure in these children was a direct consequence of emotional deprivation rather than secondary to caloric malnutrition. In the first place many of the emotionally deprived children released subnormal amounts of pituitary growth hormone on hypoglycemic stimulation. In the second place several of the children when first seen exhibited normal weight for height. This, however, is not an altogether reliable index of nutritional studies because many of the children described by Powell including those not malnourished according to this index did gain weight when they were removed from their destructive environment and hospitalized. In the new environment they gained weight in excess of that to be expected after allowances were made for this prodigious growth in stature.

The description of the children's behavior reflects that seen in famine. All had prominent abdomens, some decreased muscle mass and foul smelling stools and polyphagia and poor weight gain, so that there may have been some element of malabsorption present in many of the children. However, all of these disappeared on entering the hospital and this strongly supports the psychic factor and its effect on growth although it does not rule out temporary non-absorption and non-utilization of an essential food factor.

Apparently growth inhibition can persist for many years without permanently suppressing the capacity for "catch up" growth. Once the children were removed from their homes the children grew over large periods of time until normal weight was achieved. Whenever short stature is being evaluated, therefore, not only must idiopathic hypopituitarism come to mind but also unusual psycho-social situations at home.

Short stature may be one aspect of a continuum of adverse effects of a distorted child-parent relationship and may in fact be the first suggestion of such a distorted relationship. The growth pattern suggests that an adverse environment acting during the early critical years of childhood can be responsible for growth retardation. This report[6,7] reminds one of the growing evidence that environmental events occurring during the early critical periods of infancy can leave a permanent imprint altering both endocrine responses and behavior of the adult. In Kaufman and Rosenbloom's experiments it was separation of an infant from a good environment that led to depression. In Powell's report it was separation of a child from a bad environment that led to his improvement. This separation and deprivation are not equivalent terms.

The reversibility of growth retardation was demonstrated in Powell's study. What will happen to the emotional and mental retardation we can only learn from long term follow-up observations. Obviously treatment will almost invariably require removal of the child from the home where emotional deprivation exists. The help of psychiatrists, psychologists, social workers is essential. In some cases there may be required additional assistance from the Court of Law. Above all early recognition of adverse influences upon infants and children and their correction may prevent permanent lasting damage to the organization and function of the central nervous system in man.

L.H.N.

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Delayed Hypersensitivity In Clinical Medicine

Jenner described the reaction of immunity in vaccinated persons, in his classic monograph entitled "An inquiry into the causes and effects of variolae—vaccinee." There was a papular erythematous lesion of the skin reaching its maximum twenty-four to seventy-two hours after vaccination and disappearing without passing through a pustular stage or leaving a scar. The term allergy was introduced by Von Pirquet in 1906. The tuberculosis patients on receiving a subcutaneous injection of tuberculin reacted with fever and generalized sickness. Thus arose the concept of hypersensitivity in which an immunologic response can lead to damage. Both the immune response on re-vaccination with varicella and the Von Pirquet response on injection of tuberculin may be termed delayed hypersensitivity.

There is also an immediate type of sensitivity first described by Maurice Arthus in 1903. Four to eight hours after injecting horse serum into sensitized rabbits there developed at the site of injection, edema, hemorrhage leading to necrosis, rather than erythema and induration days later. Other forms of immediate type hypersensitivity are systemic anaphylaxis, wheal and flare reactions on testing patients with hay fever and asthma to the antigen to which they are allergic.

The immediate type reaction is a vasculitis associated with massive infiltration of the skin with granulocytes. The delayed reaction is a massive perivascular infiltration of the dermis with mononuclear cells and considerable swelling of the dermal collagen. In immediate hypersensitivity there are present circulating antibodies which can passively transfer the allergic state and they reside in one of the immunoglobulin fractions of the serum. No such humoral factor has yet been shown to cause delayed hypersensitivity but both the contact type of sensitivity and the tuberlin type allergy can be transferred by leucocyte injections.

Contact sensitivity is seen in patients with eczema due to allergy to a simple chemical compound which becomes antigenic when bound to the patients own protein. These contact reactions are erythematous vesicular and indurated reach their peak twenty-four to forty-eight hours after application of the patch, much like a tuberculin reaction.

The homograft reaction is a type of delayed hypersensitivity. The histologic appearance of the process of graft rejection reveals prominence of mononuclear cells and a near absence of granulocytes. It is the same appearance as is found when a chemical sensitizer has been applied — lymphocytic proliferation around the patch and in the nodes draining this area of skin.

Some auto-immune diseases are known to exhibit delayed hypersensitivity. A tuberculin type reaction to thyroglobulin can be demonstrated in the skin of guinea pigs in experimental auto-immune thyroiditis. Experimental auto-immune encephalomyelitis can be transferred reproducibly in guinea pigs and rats. Delayed hypersensitivity might be involved in rheumatoid arthritis because it can occur even in the presence of agammaglobulinemia. The Aschoff lesion in rheumatic fever may be a form of delayed hypersensitivity to sarcolemmal antigen. There are some diseases, however, in which the role of hypersensitivity in auto-immune disease has not yet been sufficiently defined.

There has been much speculation as to the role of delayed hypersensitivity in infection. Cells probably play a role in defense against infection. Macrophages from immunized rabbits are capable of inhibiting the growth of the tubercle bacillus to a greater extent than those from normal rabbits. Cellular immunity has now been studied against a wide range of organisms. Resistance to tuberculosis cannot be transferred with serum, but it can be transferred with peritoneal exudate macrophages and lymphocytes. However, it is not yet possible to say whether cellular immunity and delayed hypersensitivity are due to the same phenomenon or to some related but different mechanism.

L.H.N.

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The Prostaglandins: Members Of A New Hormonal System

Thirty-seven years ago, two New York Gynecologists, Kurzrok and Lieb produced strong contractions of the human uterus by instilling fresh human semen. We now know that these effects were due to the prostaglandins (PG) present in the seminal plasma. Several years later Goldblatt in England and U. S. von Euler in Sweden independently discovered and studied the strong activity in seminal plasma that stimulates smooth muscle. von Euler prepared lipid extracts of vesicular glands of male sheep and found the activity to be associated with the fraction containing the lipid soluble acids which he named prostaglandin and made extensive studies of the physiologic and pharmacologic effects of these extracts.

The next logical step was purification of a concentrate prepared from glands of icelandic sheep by Sune Bergström, a pupil of von Euler. The isolation work was greatly facilitated by the stimulating effect of PG on smooth muscle. By this method of assay and with improved isolation procedures, he isolated two prostaglandins PGE1 and PGF1 in pure crystalline form. They both had high physiologic activity on smooth muscle, but PGE1 was more active in reducing blood pressure in the rabbit.

Two more compounds of PGE type were subsequently isolated from sheep glands and others from bovine lung tissue, pancreas, brain, kidney, iris, human menstrual fluid. There appears to be strong indications of the occurrence of PG in many other tissues. The richest source known, however, remains human seminal fluid. As methods were refined and smaller and smaller amounts could be isolated in pure form, metabolites of the PG were also isolated and finally it became clear that lungs have a high capacity to inactivate the PG.

The fate of small amounts of labelled PG when injected intravenously into rats showed that 50 per cent of the isotope had been excreted in the urine in forty hours and 10 per cent in the feces by way of the bile. There were transient high concentrations in kidney, liver connective tissues and myometrium.

Once the structure of the primary PG has been elucidated the next logical step was to seek their precursors. It soon became clear by a fine series of biochemical studies that the prostaglandins are formed in a facile enzymatic sequence of reactions in several different tissues from members of the group of essential unsaturated fatty acids and the one which has proved the most active is linolenic acid which we remember as important in inhibiting platelet adhesiveness.[2] It would be expected, therefore, that essential fatty acid deficiencies in animals and man could prevent synthesis of PG.

Most of PG's have potent biologic activity of some kind. The typical effect on the circulation is peripheral vasodilatation of small arteries and a reduction of blood pressure even in nephrectomized dogs. They also strongly antagonized the hypertensive effects of epinephrin and norepinephrine.

Some prostaglandins the PGE type inhibits strongly strips of myometrial muscle, of non-pregnant females. The PGF compounds on the other hand show stimulatory action that varies in degree during the menstrual cycle. A complex action also occurs in the fallopian tubes, the inner third contracts, the outer third relaxes. The development of pure compounds and more sensitive techniques have allowed study of their effects in pregnant women. Very minute amounts cause onset of uterine activity similar to normal activity during labor. Deposition of PG in the vagina has similar effects. In view of the large amounts present in seminal fluid, it seems possible that sufficient PG can be absorbed from the vagina to influence strongly in some instances the motility of the pregnant uterus.

We know that lipolysis can be rapidly activated by epinephrin, norepinephrin, glucagon, ACTH, TSH and vasopressin. PGE strongly inhibits action of epinephrin in very small concentrations. It also blocks vasopressin induced increase in water permeability of the toad bladder. Bergström found that PG's can antagonize every one of the hormones listed above. They also affect platelet aggregation and adhesiveness much as linolenic acid does.

It seems that PG can be released from nerves, brain, adrenals, diaphragm and fat pads by stimulation of the afferent nerves or by hormones and certain drugs. Apparently all cells thus far studied can release fatty acid precursors of PG that would rapidly be synthesized into PG by microsomes. Bergström believes that the PG thus formed might act as a general feedback regulator and have some role in neuronal activity.

From all this work it is obvious that PG can exert marked effects on various important physiologic processes. More work is obviously needed to ascertain their specific roles in the living organism. Are they mainly intracellular metabolic modulators or are they systemic hormonal regulators or both?

L.H.N.

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Combatting The Cigarette Habit

In 1964 the Surgeon General's Committee issued a report indicting cigarette smoking as a cause of lung cancer and other diseases. Surgeon General Stewart has estimated that 275,000 deaths each year can be attributed to the smoking habit. Some of the Health, Education and Welfare (HEW) departments recent findings indicate further that the importance of smoking as a contributory factor in heart disease is even greater than has been suspected—that among men-smokers the death rate from coronary heart disease is 70 per cent higher than among non-smokers. Frightening statistics of this sort can be used to shake the smokers com-

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	ROBITUSSIN	ROBITUSSIN A-C	ROBITUSSIN-DM	ROBITUSSIN-PE
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COUGH SUPPRESSANT		●	●	
ANTIHISTAMINE		●		
LONG-ACTING (6-8 HOURS)			●	
NASAL, SINUS DECONGESTANT				●

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placency especially since many smokers are already anxious about this habit, but how.

On June 2nd, the Federal Communication Commission (FCC) issued a ruling named the "fairness doctrine" which holds that broadcasting stations must make time available for discussion of both sides of a controversial issue. The ruling was directed at no product except cigarettes. The Federal Trade Commission (FTC) and HEW say in effect that cigarette smoking is an exceedingly dangerous habit which has been popularized and re-inforced by advertising campaigns portraying the "lethal weed" as harmless and mild and subtly associating smoking with joys of sex, propriety and high adventure. Both reports called for warning in advertising as well as on the package to show the tar and nicotine content of the cigarette smoke. The FCC report was clearly an opportunity for all health forces to unite and attempt to neutralize the subtle deception in cigarette advertising by having an opportunity to present the true facts on the air without cost.

Suddenly the National Clearing House for Smoking and Health and the American Cancer Society (ACS) and the American Heart Association and other groups saw an opportunity to get lots of free air time for their anti-smoking "spot" announcements and programs. Previously TV broadcasters had been chary in offending their cigarette advertisers by cooperating in anti-smoking campaigns, although they had often carried views and discussion programs dealing with the smoking and health issue. Since the "fairness doctrine" ruling, the ACS has provided a list of its anti-smoking spots and programs for those who elect to follow the FCC discussion.

The demand for anti-smoking material has become heavy. One TV network has asked ACS for more prints of its spot announcements than it can supply. Most of the anti-smoking material provided by the ACS and other agencies use low-pitched persuasion which avoids the scare techniques. The working assumption is that most people know smoking is harmful, but need to be reminded and made constantly aware of this threat to their health. The Ash-tray is a twenty second ACS spot showing cigarette butts disappearing from an ash-tray while a violin plays softly in the background. A voice says "the moment you stop in most cases the effects of smoking will begin to reverse themselves until your lungs are nice and clear again."

"Is smoking worth it" is a sixteen minute ACS film which reviews the evidence linking lung cancer and cigarette smoking. Some ACS material is prepared especially for very young viewers. Huffless Puffless Dragon is an eight minute animated cartoon showing an unequal struggle between Drag Knight who does not smoke and Drag Goon who does.

The "fairness doctrine" has not been taken by the broadcasters lying down. They are alarmed for a variety of reasons. One is the effect the ruling will have on cigarette advertising which in 1966 accounted for seven per cent of TV revenue. A significant amount of valuable time will have to be given away free. They are going to court insisting it is an unconstitutional abridgement of freedom of the press and "due process." The broadcasters also contend that the ruling violates a congressionally imposed moratorium on health warnings in cigarette advertising. Finally that the ruling cannot be logically limited to cigarettes and may be extended to other commodities such as automobiles, alcoholic beverages and pesticides.

We must not underestimate the legislative potency of the tobacco and broadcasting industries. They are not ready to preside at their own demise. Congress could nullify the ruling and there have been attacks upon it by representatives from North Carolina and Virginia where tobacco is grown and processed. The broadcasting industry may encourage congressional interest in intervening, through editorial criticism of the ruling by newspapers whose owners may also have broadcasting stations. In its effort to avoid strong legislation the tobacco industry played an important card. It asked Congress to give it a chance at self regulation under the tobacco and broadcasting industries new cigarette advertising codes.

The FTC now says, however, that the codes have done little to prevent abuses at which they were ostensibly directed, such as enticement of minors to take up smoking. The cigarette commercials are still shown at hours where there is a large juvenile audience. The average teen-ager sees more cigarette commercials than the average American does, says FTC. In short FTC has asserted that the industry codes have been a sham, that the warning on the cigarette package has been largely ineffectual and that young people are heavily exposed to the seduction of cigarette advertising.

Many in Congress, however, do believe that it is necessary to have some kind of antidote to the messages of the commercials which imply that cigarettes can be smoked without harm. But is countering the advertising a sufficient answer? We need only to recall that only wine and beer may be advertised on the air but this has not prevented the progressive increase in the consumption of hard liquor. What do we know about how the smoking habit is formed and becomes ingrained? Is advertising the most potent cause or are there other social factors involved which would foster the habit even if all advertising were prohibited? Cigarette smoking as a national habit may very well outlive any who prophecy its demise. But its enemies are growing stronger and the FCC ruling in the fairness doctrine has given them a new weapon. We must still learn how the habit starts, what keeps it going and when is the best time to combat it, and by what means.

L.H.N.

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Erythema Multiforme—Dermal Hypersensitivity To Herpes Simplex Virus

Dermal hypersensitivity in recipients of inactivated measles virus following injection of attenuated live measles virus or injection with natural measles virus is now well documented. The victims develop a form of delayed hypersensitivity which varies from local induration lasting up to four months to systemic involvement with swollen joints and even pneumonia in some instances.

Now we find that erythema multiforme can occur recurrently, each attack being preceded by clinical herpes simplex. Such a historical sequence has been noted many times before and is exemplified by the case reported by Shelley.[1] Nasermann[2] found 15 per cent of all cases of erythema multiforme were regularly preceded by an attack of herpes simplex. Serologic tests including neutralizing complement fixation, agglutination and precipitation gel diffusion, disclosed nothing unique in these individuals. This raises the question as to whether herpes simplex virus could possibly be the antigen.

It is well known that inactivated herpes simplex antigen may at times produce a delayed papular tuberculin type response in intradermal testing with recurrent herpes simplex.[3] Söltz-Szöts[4] reported a patient in whom erythema multiforme developed while the patient was receiving herpes simplex vaccine for the treatment of recurrent herpex simplex.

Shelley in his case repeatedly reproduced the local vesiculobullous lesion of erythema multiforme by intradermal injection of commercially prepared but as yet experimental herpes simplex antigen. This vaccine had already been found ineffective in the treatment of recurrent herpes simplex. No vascular or bullous reactions were noted by these workers and in Shelley's control group of fifteen the typical delayed hypersensitivity reaction in the form of a papular response only was seen. Thus the vesicular reaction may be viewed as evidence of a specific type or degree of hypersensitivity, limited to patients with post-herpetic erythema multiforme.

Two other of Shelley's patients had sensitivity not to herpes simplex antigen but to sulphonamide and adenocarcinoma of the sigmoid colon. These patients had no history of herpes simplex. Obviously since erythema multiforme can be caused by sensitivity to many antigens the vesicular skin test with herpes simplex antigen could help to differentiate this from other causes.

It is important to realize that herpetic erythema multiforme may be more common than we suspect from the history since many of the imputed causes may simply serve to trigger inapparent or hidden herpes simplex. Thus menses or pregnancy might activate herpes simplex of the vagina or vulvar area and in turn cause erythema multiforme in an appreciable number of patients. In this connection it should be recalled that nearly one in five hundred Papanicolaou smear tests show intranuclear inclusion suggestive of herpes simplex infection.

The oropharynx, conjunctive, penis or indeed the central nervous system may be other occult reservoirs of the virus which may be activated by a welter of diverse diseases and thereby induce erythema multiforme. It is evident that only a mass skin test screening of erythema multiforme patients will permit an estimate of the actual role played by herpes simplex in the production of this disease. However, it will require a potent standardized antigen rather than the crude weak one formerly used.

Erythema multiforme is, however, not the only post-herpetic syndrome which has been described. Shearer and Finch[5] recently reported a severe periodic organic psychosis appearing two to eleven days after each attack of herpes simplex. One patient is reported suffering from recurrent attacks of herpes simplex as a result of an inability to form adequate amounts of specific I_gA immunoglobulin.

Heretofore the cause of erythema multiforme was elusive and in most instances went unrecognized. We have suspected drugs or malignancy, but the clinical picture has precluded challenges with drugs and this has prevented study. Our knowledge of the disease lagged because it could not be produced experimentally. Now the fact that inactivated herpes virus antigen can reproduce the disease locally gives us an experimental model for further studies and offers hope that specific tumor and drug antigens can be prepared for this type of testing.

Much remains to be done to delineate the immunologic parameters of erythema multiforme when the viral antigen is introduced into the skin. The herpes antigen which so far has had indifferent success as a therapeutic vaccine may find a more distinguished career as a diagnostic test.

L.H.N.

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LSD And The Law

There is very little doubt that the use of LSD is spreading, that its serious consequences are coming to light and that society is becoming concerned about its illicit, unintelligent and indiscriminate use. The incidence of illicit use and the effects of the drug are not entirely known. Dr. Timothy Leary estimates that 10 to 15 per cent of all college students have experimented with LSD. On the other hand Dr. D. L. Louria,[1] Associate Professor of Medicine at Cornell University College of Medicine states that one per cent is a more accurate estimate. He cites the chilling fact that in the past 18 months over 130 patients have been admitted to Bellevue Hospital with LSD psychoses or with chronic schizophrenia or schizoid personality, exacerbated by LSD ingestion.

Profound terror, uncontrolled aggressiveness, and even attempted homicide or suicide are the symptoms that are said to accompany the uncontrolled use of the drug in certain persons. However, LSD when carefully administered in experimental medical centers seems to show some promise as an adjunct in the treatment of chronic alcoholism, schizophrenic children and psychoneuroses. Thus, Medicine is presently endeavoring to assess the toxicity of these compounds. It is also exploring their potential as therapeutic agents. Medicine cannot prevent the spread and illicit use of the drugs. It is the Law that has been called upon to stem the tide of illicit use and at the same time it must make provisions to permit and encourage the carefully controlled research that is essential if the many questions about LSD are to be answered.

The federal law is conceived on a relatively sound philosophical basis. The appropriate law is found in the Federal, Food, Drug, and Cosmetic Act,[2] which provides provisions to control illicit trafficking in the hallucinogens. It states that sending or transporting the drug subjects the sender to punishment, but possession for ones own use or the use of ones own animals cannot be punished under this federal law. Clearly the federal law is aimed at the trafficker. But it does not enable federal agents to act on possession or use. In consequence the federal agents are obliged to team up with state officials and the consequence can be very harsh state punishments in certain states and little or none in others.

Besides this confusion on a federal level is the fact that two different agencies are responsible for controlling research with LSD. The Food and Drug Administration (FDA) has decided to brand LSD as a new drug and this requires that an I.N.D. (investigational new drug application) be filled out before any research can proceed. The FDA also polices the illegal manufacturing of the compound. There is, however, a goodly supply in the possession of the National Institute of Mental Health for research since Sandoz Pharmaceutical's total supply has been turned over to this agency. The researcher who desires to work with LSD must first have his research approved by the NIMH and then after the research has been done, must work with the FDA as well as the Institute in filing an acceptable application. The result of the control by the two agencies has led to a good deal of confusion and limitation of research.[3]

Since the problem of treatment or punishment devolves upon the state jurisdictions, it is not surprising how varied they could become from state to state. The Massachusetts legislature, for example, has responded to the problem quickly and rigidly by laws whose philosophy is not treatment but punishment. The law has seen fit to label LSD and the other hallucinogens as narcotics and to consider LSD cases in the same class as the heroin addict.[4] Under the Massachusetts law, whosoever is present where LSD is illegally kept whether or not he knows he is in the presence of illegally kept LSD, may be subject to a five year sentence in the State Prison. A college student who induces his girl friend or a fellow student to try the drug risks 10 to 20 years in the State Prison and 20 to 50 years for a second offense.[3]

In Massachusetts, possession of LSD carries up to three and half years in the State Prison[5] and the law does not encourage the seeking of medical help either by the LSD user or the heroin addict. According to the law the users are criminals not sick people requiring medical treatment. The relentless aim of the law extends to the doctor's office or hospital who is treating a chronic user of these compounds. The patient must be reported to the Department of Health within 72 hours of the first treatment, a statement in duplicatec ontaining the name, address, height, weight, date of birth and color of the hair of user, the place of treatment and the name of the drug used. It also provides such information shall be made available for the use of any agency of the Commonwealth for the United States may require it.[6]

New Hampshire on the other extreme has no legislation controlling the illicit use of LSD and at this moment State officials are powerless to deal with the problem at all.[3] Connecticut is somewhere in between. It relegates control of LSD in the Division of Consumer Protection. This agency is obviously confronted with an incompatible combination of responsibilities. Apparently the Law is trying with questionable success to regulate and control the illicit use of these drugs. Because of the urgency of the situation, legislative expedience has replaced careful consideration of the many and complex issues involved.

College officials are also beginning to act in their way. They are beginning to realize the need for control of these dangerous substances. Dean Monro of Harvard issued a statement "if a student is stupid enough to misuse his time here fooling around with illegal and dangerous drugs . . . he should leave college and make room for people prepared to take good advantage of the college opportunity." This statement mentioned above was accompanied by a full and excellent outline of the medical risks involved prepared by Dr. Dana L. Farnsworth. Whether this kind of warning of the drug danger will fare any better than all the warnings on the dangers of smoking to health, remains to be seen. It is probably too simplistic to believe that the causes of drug addiction are so superficial that warnings such as that of Dean Monro will have any significant impact on the alarming spread of LSD.

L.H.N.

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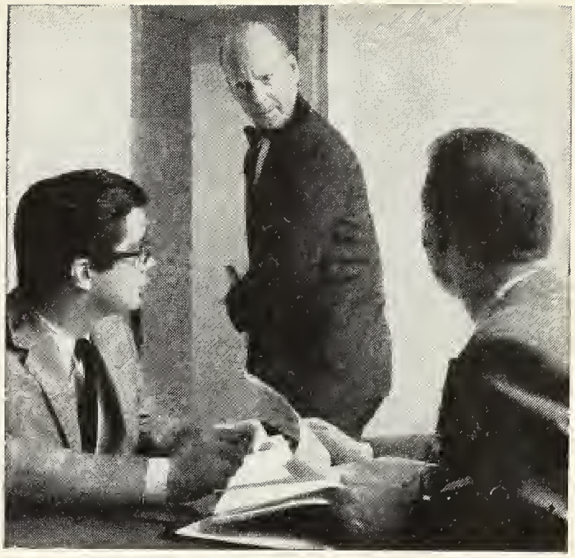

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Fertility Issue

Introduction

Robert H. Glass, M.D., *Guest Editor*

The last decade has witnessed a marked improvement in our ability to treat certain types of infertility. Prior to 1958 the anovulatory woman had little chance of conceiving despite treatment with a wide range of medications. In 1958 Gemzell, Diczfalusy and Tillinger introduced the use of human pituitary extract to induce ovulation in women. Since that time numerous pregnancies have been achieved through the use of either human pituitary extract or human menopausal gonadotropin extracted from the urine. In addition, a synthetic product, clomiphene citrate has been extensively utilized in the treatment of anovulation.

Progress also has been made in other areas of infertility during the past ten years. It has been shown that there are cases of otherwise unexplained infertility which may be due to spermatozoal antibodies that are found in the serum of some infertile women. In a number of these cases the antibody titer may be reduced by appropriate treatment with resultant increased chance of pregnancy.

Treatment of male fertility is still a difficult problem. Attempts to raise sperm counts by use of gonadotropins, clomiphene or steriods have not produced consistant results. However, a number of infertile men with varicoceles have produced pregnancies after varicocelectomy.

In this issue of "Connecticut Medicine," we have reviewed some of the current concepts in fertility with emphasis on the more recent developments. Despite the gains of the last decade, there are still a number of couples who do not achieve a pregnancy. The physicians ability to help these couples will be enhanced by a clear view of the adoption facilities available in the State of Connecticut and these are outlined in the article by Mr. Nathan Sklar.

I would like to thank all the contributors to this issue who have so willingly shared the benefits of their experience.

Investigation Of The Infertile Couple

Robert H. Glass, M.D.

■ The aims of an infertility investigation should be twofold. The first is to discover and to treat the factors interfering with fertility. However, only 30-40 per cent of couples attending an infertility clinic achieve a pregnancy and therefore it is important to consider what can be accomplished for the remaining 60-70 per cent who will remain infertile. The aim for this latter group is to provide them with a thorough evaluation and sympathetic counsel so that they are able to plan for a future which may include adoption of children. Both these aims of an infertility investigation can be achieved by a systematic study of the reproductive potential of the male and the female partner.

Usually the female will initiate the study by consulting a doctor who should assume responsibility for the conduct of the overall investigation. If this doctor is a gynecologist he may feel that the major portion of the evaluation of the male should be performed by a urologist interested in infertility.

At the time of the first interview, the patient should be told about the specific procedures that will be performed and cautioned that a thorough investigation may require several months. At the Yale Infertility Clinic the patient is given a printed form which briefly discusses the major diagnostic tests used in an infertility workup. This instruction sheet is used to supplement, not to replace, the doctor's discussion.

History And Physical Examination

A complete personal and family history should be obtained with emphasis placed on those areas pertinent to reproduction. The length of time that the couple has practiced unprotected sexual relations should be noted. As a rule, failure to con-

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ceive after one year of unprotected relations is considered justification for the initiation of an infertility investigation. Infrequent occurrence of relations may be a cause of infertility. A frequency of 2-3 times a week is considered adequate exposure. Problems such as impotence may be uncovered during the recording of the history.

A history of pelvic inflammatory disease, tuberculosis or appendicitis suggests that tubal disease or pelvic adhesions may be a significant factor. Anovulation is often marked by irregular menses.

It is well to inquire whether the patient has undergone a previous infertility investigation. Unnecessary duplication of tests can be avoided by obtaining the records of previous workups.

The physical examination should check all body systems and the doctor should be alert to discover abnormalities which are unrelated to the primary complaint of infertility.

It has been our policy to obtain Papanicolaou smears from all patients but in the infertility population of relatively young, largely nulliparous women the number of positive smears will be quite small. The patient's urine is tested for sugar and protein. Either a hemoglobin or hematocrit is obtained. If there is evidence by history or physical examination that the patient has had pelvic inflammatory disease a serology, white blood cell count and sed rate is also obtained. It has not been our policy to routinely order chest X-rays on every patient. A chest film is ordered if there is a history of Tbc contact or if the patient comes from an area where tuberculosis is a significant problem.

Basal Body Temperature

During the first visit the patient is instructed in the method for recording her basal body temperature (BBT). She is provided with charts for recording the temperature and in addition is told to record any changes in her daily routine such as illnesses. Vaginal bleeding and occurrence of sexual relations should be noted on the charts. The temperature, which must be recorded on awakening and prior to any activity, can be obtained with an ordinary oral or rectal thermometer or with specialized thermometers which cover only a few degrees and therefore are easier to read. A rise of 0.6°F. or more at the midcycle, sustained for 10-14 days prior to menses, is strongly suggestive of ovulation in that cycle. A review of the charts of 3-4 months will allow the doctor to confirm that sexual relations are occurring in proximity to the time of ovulation. It is well to discourage patients from having sexual intercourse dictated by the temperature chart. The rise in temperature is only an approximate guide to ovulation which may in fact occur 48-72 hours prior to the rise. Exposure 2-3 times a week over the course of a number of months will usually provide a few opportunities for optimal matching of ovulation and intercourse. If the BBT is biphasic over a 3-4 month period and ovulation is also suggested by endometrial biopsy then the patient may discontinue the recording of her temperatures.

Semen Analysis

A semen analysis should be performed at the onset of an infertility investigation. The specimen is best obtained by masturbation into a clean wide mouthed jar, and the analysis should be performed within 3-4 hours. A sperm count above 20,000,000/cc is within the normal range. A sperm count below this figure may be associated with successful pregnancies but statistically the chances of pregnancy are poorer than with higher counts. Sperm motility is even more important than the sperm count.[3] Forty per cent or more of the sperm should be progressively motile. Poor sperm motility may be caused by a varicocele of the testes which is amenable to surgical treatment. Abnormal sperm morphology may be a cause of infertility. Semen volume greater than 6 cc or less than 2 cc may contribute to infertility. The former may be treated by artificial insemination using split ejaculates. The ejaculate is collected by masturbation in 2 separate jars. The jar containing the higher sperm density is used for inseminating the women.

Any abnormality of the initial semen analysis should be confirmed by examination of a second specimen obtained after three days of continence. Repeated abnormalities of the semen suggest the need for a thorough urological investigation.

Tubal Patency

Tubal patency tests should be performed during the proliferative stage of the menstrual cycle, 2-4 days after the cessation of the menstrual flow. A test performed at mid-cycle introduces the theoretical risk of blowing a fertilized ovum out of the tube into the peritoneal cavity. Tests performed in the secretory phase of the cycle must contend with a thickened endometrium which may occlude the tubal opening into the endometrial cavity and thus produce a false impression of tubal closure.

The three commonly used tests for tubal patency are the Rubin's test, hysterosalpingography, and dye insufflation of the tubes under culdoscopic visualization. The Rubin's test utilizing co_2 is the least accurate of the three. Failure of passage of gas may be caused by tubal spasm rather than tubal pathology. However the simplicity of the test warrants its continued use as a primary screening test for tubal patency. The cervix is wiped clean with aqueous blue zephirin and a cannula fitted with a rubber olive near the tip is inserted into the lower cervical canal. The cannula is connected to a CO_2 insufflation device and a kymograph. The gas is slowly turned on until it is flowing at a rate of 30 cc/minute. The CO_2 should flow through patent tubes at a pressure between 80-120 mm. Hg. It may be necessary to raise the pressure to 200 mm. for a brief period to overcome tubal spasm, at which point the pressure will drop to 80-120 mm. Evidence of patency in addition to that shown by the pressure recordings can be obtained by listening with a stethoscope over the lower abdomen for the bubbling noise created as the gas flows out of the tubes. Shoulder pain experienced by the patient when she sits up at the completion of the test is suggestive evidence that CO_2 has entered the peritoneal cavity. This very valuable sign of tubal patency is lost when the test is performed under general anaesthesia. Our practice has been to perform the Rubin's test as an office procedure. Failure of CO_2 passage indicates the need for further diagnostic investigation of tubal patency.

Hysterosalpingogram using ethiodized oil* is best performed with the aid of fluoroscopic visualization with an image intensifier. A 24 hour follow-up X-ray film is extremely helpful in diagnosing tubal pathology and pelvic adhesions. Both adhesions and fimbrial occlusion of the tube may produce pooling of dye on the 24 hour film in contrast to the homogenous distribution of dye found in a normal pelvis. With the use of an image intensifier no more than five X-ray films should be necessary for adequate evaluation. The common practice of taking multiple oblique and stereoscopic views adds little to the diagnostic value of the hysterosalpingogram and subjects the patient to added radiation.

Both CO_2 insufflation and hysterosalpingography may give erroneous results. Buxton and Southam reported that 8 of 71 patients in whom tubal closure was indicated by both tests became pregnant without surgical treatment. Because of this possibility of error a decision for tubal plastic surgery should be made only after culdoscopic examination of the pelvis has confirmed the diagnosis of tubal pathology. At the time of culdoscopy indigo carmine is injected into the cervical canal and the passage of dye through the tubes is noted. Flow of the dye from the distal end of the tube is proof of patency. However, even this procedure may result in an error in diagnosis. On occasion no dye is seen to flow from the tubes but at laparotomy the tubes are found to be patent.

The results of surgical treatment of occluded tubes have been disappointing.[5] Cases in which the pathology is peritubal adhesions and in which the tubes are intrinsically normal offer the best prognosis.

Post Coital Test

The post coital test (P.C.T.) provides information concerning both the female and the male partner in an infertility investigation. The P.C.T. should be performed at mid-cycle because the cervical mucus is most abundant at the time of ovulation. The woman is instructed to remain in bed for 30 minutes following sexual relations and to refrain from taking a post coital douche. It should be noted that women desirous of pregnancy should always avoid immediate post coital douching. Eight to sixteen hours after sexual relations a specimen of endocervical mucus is removed with the aid of a nasal polyp forceps. Ovulatory mucus is clear, thin and can be stretched out to a length greater than 10 cm. (spinnbarkeit). Thick, tenacious, cloudy mucus containing an abundance of white blood cells indicates either that the specimen has not been obtained near the time of ovulation or that there is an infection of the endocervical glands. If repeated P.C.T. show poor, thick mucus despite evidence of ovulation, the patient should be treated with diethylstilbestrol 0.1 mg. daily for 3-4 months. The estrogenic stimulation will increase the amount of cervical mucus and, in the process, often decrease its viscosity and cellularity. Failure to respond to the treatment can often be overcome by increasing the dosage of diethylstilbestrol to 0.2 mg. daily. These dose levels are lower than those which will inhibit ovulation. Lack of response to diethylstilbestrol suggests the presence of cervical infection which is often difficult to cure. The most widely used therapy is the vaginal instillation of antibiotic creams following determination of the bacterial flora by cervical cultures. Electrocauterization of the cervix should be used only in refractory cases and then used only superficially to avoid destruction of the cervical glands.

The interpretation of the male factor in the P.C.T. is subject to greater variability. There has been disagreement as to what constitutes a "good" P.C.T. and estimates range from one motile sperm per high power field (HFF) to over 20 motile sperm/HPF. In our experience a P.C.T. which contains 1-20 motile sperm/HPF merely indicates that the couple is having adequate coitus and that the husband is not azospermic.[2] At this level the number of sperm present in the P.C.T. do not provide an indication of the sperm count.

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* Ethiodol—E. Fougera and Co., Inc. Hicksville, Long Island, N. Y.

However, in our series, a P.C.T. containing over 20 motile sperm/HPF was invariably associated with a sperm count above 20,000,000/cc and it is only in these cases containing over 20 sperm/HPF that a semen analysis can be safely omitted.

A P.C.T. which contains no sperm on repeated occasions suggests azospermia or failure to achieve intromission. A semen analysis will diagnose the former and the presence of an intact hymen will suggest the latter diagnosis. In addition there are rare cases of failure of the ejaculatory mechanism despite adequate intromission and cases of retrograde ejaculation into the bladder. Both these conditions require the consultation of a urologist.

Patients have become pregnant in the same cycle in which they had a P.C.T. which contained no sperm.[1] This again emphasizes the need to interpret the P.C.T. with caution.

Endometrial Biopsy

Endometrial biopsy provides the most reliable indirect evidence of ovulation. The optimal timing of the biopsy has been disputed. A biopsy performed a few days before the expected menstrual period generally provides excellent tissue for histologic study. However premenstrual biopsies run the risk of interfering with an early pregnancy and therefore some advocate taking the biopsy on the first day of the menstrual flow. Tissue obtained at the onset of flow is often more difficult to interpret because of the disruption caused by menstrual changes. Waiting for the onset of bleeding before taking a biopsy may not always protect against the possibility of interrupting a pregnancy. It is well known that there may be some bleeding at the time of an expected menstrual period during the course of an early pregnancy. Another difficulty with menstrual biopsies is that the onset of flow may occur at a time when it is inconvenient for either the doctor or the patient to obtain a biopsy. It has been the policy at the Yale Infertility Clinic to do premenstrual endometrial biopsies 2-5 days before the anticipated menses. A recent review of our experience showed that patients biopsied during the cycle in which they became pregnant had no higher abortion rate than what is reported for the infertility population as a whole. This problem can be avoided entirely by suggesting that the patient use mechanical contraception during the month in which the biopsy is to be obtained.

Prior to inserting the biopsy curet a bimanuel examination should be performed primarily to determine the position of the uterine fundus. A single tooth tenaculum is applied to the anterior lip of the cervix. In some cases of marked anteversion it may help to straighten the uterine axis if the tenaculum is applied to the posterior lip. The curet is then passed through the cervix and a single strip of tissue is obtained from high on the anterior fundal wall. Tissue obtained from the lower uterine segment will not reflect accurately hormonal influences. The endometrial tissue should be placed immediately in Bouin's solution. Biopsies are performed in the office and only rarely is it impossible to obtain a specimen. In cases where there is some difficulty in passing the curet it is helpful to do a paracervical block. The use of a D and C to obtain tissue for dating of the endometrium is seldom if ever required.

The endometrial biopsy provides information beyond the question of whether ovulation has occurred. Secretory endometrium may be present but its stage of development may be out of phase with the date of the cycle. If repeated biopsies show that the endometrium lags 2 or more days behind the picture expected for that date then a diagnosis of inadequate luteal phase can be made.[4] Treatment consists of progesterone or a progestational compound (Provest* one tablet daily) for eight days starting three days after the low point in the basal body temperature.

The reader is referred to the article by Dr. Kase in this issue for a complete discussion of the investigation and treatment of anovulation.

Spermatazoal Antibodies

A test for the presence of agglutinating antibodies to sperm in the serum of infertile women has now become part of the routine investigation performed in our clinic. For a complete discussion of this topic the reader is referred to the article by Dr. Olson in this issue.

Culdoscopy

No infertile couple should be told that they are free of pathology until a culdoscopy has been performed. In a series of 97 patients from our clinic in whom no cause of infertility could be found culdoscopy led to a diagnosis in 37 per cent. In most series endometriosis and pelvic adhesions are the two most common unsuspected diagnoses revealed by culdoscopy. It is now our practice to suggest culdoscopy to all patients who do not conceive within six months of the completion of an infertility work-up which reveals no abnormalities. Culdoscopy is performed even earlier if the patient has an abnormal hysterosalpingogram. The fertility potential of the husband is evaluated prior to culdoscopy and the procedure is not indicated if the husband is azospermic, or severely oligospermic.

In almost all instances the patients are prepared for laparotomy in case the culdoscopy should reveal abnormalities that can be treated surgically. Culdoscopy is performed with the aid of either para-cervical block or continuous conduction anaesthesia. There are two advantages to the use of paracervical block. If the culdoscopy shows a normal pelvis the patient may leave the hospital the same day. If surgery is required it can be performed under general anaesthesia without the complicating factor of a simultaneous conduction anaesthetic. Alternatively it is possible with continuous conduction anaesthesia to raise the level of the anaesthetic so that it will be sufficient for the laparotomy.

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* Upjohn Co.

During culdoscopy indigo carmine is injected through the cervix to test for tubal patency.

Complications of culdoscopy are infrequent. Rectal perforation occurs in 1-2 per cent of cases but in the author's experience this has never caused morbidity. Delayed bleeding from the vaginal puncture site is easily controlled by a figure of eight suture. Rarely bleeding may be caused when a poorly placed trochar causes trauma to the posterior surface of the uterus.

Inability to insert the culdoscope into the peritoneal cavity usually signifies dense pelvic adhesions and is in itself an indication for surgery.

The view through the culdoscope may not always correspond to that which is seen at surgery. Stuermer reported that 5.9 per cent of culdoscopy diagnoses could not be verified at laparotomy. This figure should not detract from the established value of culdoscopy in the investigation of infertility.

Psychological Factors

The relationship between the central nervous system and reproduction has been convincingly demonstrated in lower animals. Gonadotropin releasing factors that control pituitary secretion have been isolated from the hypothalamus of a number of species. External stimuli such as light may exert influence on the estrous cycle through the mediation of the pineal gland.

In man there are psychological derangements which can interfere with reproduction. Impotence and hypothalamic amenorrhea are the two most obvious. There are a number of case reports in the literature claiming cures of infertility by the use of psychotherapy[6]. However it is still unknown how often unexplained infertility may be secondary to psychological factors. Buxton and Southam reported that 6 per cent of the pregnancies in their group of patients occurred between the time the women phoned the clinic for an appointment and their first visit. Sixteen per cent of the pregnancies occurred within one month of the first clinic visit. Buxton and Southam suggest that this represents evidence of the influence of psychological factors on fertility.

The doctor handling infertility problems must be alert to the psychological problems of his patients but he must also realize that the vast majority of infertility patients are as adequately adjusted as their more fertile neighbors.

There are many unanswered problems in the field of infertility. Many couples will go through life without conceiving in spite of being apparently normal. Our deficiencies in knowledge should not dissuade us from offering each couple desirous of pregnancy the very best care available. This requires that each couple receive a systematic, complete investigation of the reproductive potential of both the male and the female partner.

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Medical Induction Of Ovulation In Anovulatory Infertility

Nathan Kase, M.D.

■ As a result of investigations culminating in clinical trials carried out over the past decade, the fundamental mechanisms of ovulation in the human female have come under direct therapeutic control. The efficacy of a variety of contraceptive hormonal regimens attests to the precision of our understanding of ovulation physiology. Equally significant is the fact that stimulation of ovulation by medical means is also a clinical reality. In the absence of correctable disease to which anovulation is secondary, for the first time the responsible physician can do more than temporize while hopefully awaiting the spontaneous return of normal function. However, the usefulness of ovulation inducing drugs may be severely limited unless the hazards of their application are minimized or avoided. This report summarizes the Yale-New Haven methods and results of Clomid and Pergonal therapy of anovulatory infertility. During the years of drug evaluation, criteria for patient selection and a program of drug administration have been evolved which reduces side effects to a clinically acceptable, though not optimal frequency and yet retains a high success rate in terms of induced pregnancies.

Clomid

This recent approved drug, 2-P-(2-chloro-1-2 dyphenyl vinyl) phenoxytriethylamine dihydrogen citrate, supplied by William S. Merrell Company has been used in over one hundred cases of anovulatory infertility in this clinic. A detailed description of its use in 81 cases is the subject of a forthcoming report. After thorough diagnostic workup absence or insufficient frequency of ovulation was the only discernible cause of infertility. Because underlying pathology could not be verified, the patients were classified symptomatically:

1. oligo-amenorrhea: 52 patients had prolonged intermenstrual intervals (from 42 days to six months). The reduced frequency of ovulation was considered incompatible with ease of conception.

2. amenorrhea: 22 patients had absent menses for longer than six months (6 months to eight years). A single case of primary amenorrhea was included.

3. inappropriate lactation syndromes: seven patients (one del Castillo syndrome, six Chiari-Frommel patients) were treated. None had demonstrable central nervous system disease.

Initial workup ruled out thyroid, adrenal or organic CNS disease. Isolated pituitary-ovarian dysfunction of varying severity was the basic defect in these cases. Sixty patients had biologic evidence of estrogen production. In 15 cases without estrogen. ten had undetectable urinary gonadotropins. No case of ovarian failure was treated. Prior unsuccessful treatment included cortisone or derivatives (29 patients), wedge resection of ovaries (nineteen), cyclic estrogen and/or progestin (38) and long standing thyroid treatment (16 cases).

Initial Clomid treatment consisted of 50 mgm. (one tablet) daily for three or five days depending on the amount of estrogen activity present and ovarian size. In the event of preceding menses, the drug was administered starting day five of the cycle. Amenorrheic individuals received cyclic induction of menses preliminary to Clomid. If menses or ovulation was not achieved in the first three treatments, dosage was increased monthly to a maximum of 150 mgm. daily for five days. Prior to each course, patients were checked for side effects and residual ovarian enlargement. Basal body temperature charts were kept throughout treatment. After a pattern of dose dependent ovulation was established, patients were instructed in appropriate timing of intercourse.

Of 346 treatment cycles, 149 or 43 per cent were ovulatory. 60.5 per cent patients ovulated at least once on medication. Twenty-three pregnancies occurred in 21 patients. Twenty-six per cent of patients became pregnant on therapy. However, the per cent of induced pregnancies per induced ovulatory cycles was 15.4 per cent. Significantly the greatest success occurred in the first three treatment cycles. Furthermore, twenty pregnancies were in the oligo-amenorrheic group. All but one pregnancy occurred in women with biologic presence of estrogen production prior to

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therapy. Clomid success was independent of previous failure with other modalities.

Timing of ovulation following a Clomid course was consistent for each patient. While the interval between stopping drug and ovulation ranged from zero to three weeks, 90 per cent of ovulations were noted between 7 and 14 days after Clomid administration.

No multiple births (though about 10 per cent was expected[2]) or congenital anomalies have appeared in this series to date. Abortion incidence (two) has also been surprisingly low.

The major side effect of treatment has been ovarian enlargement, either unilateral or bilateral, greater than 6 cm. diameter, which appeared in seven patients. In none was hospitalization required for pain or rupture. However, the presence of this reaction indicated possible hypersensitivity and subsequent dosage was either postponed or not increased. Other effects included vasomotor symptoms, bloating and breast tenderness. These were sporadic and did not necessitate dose modification by their presence.

On the basis of these results and other reports[3-5] Clomid appears to be a relatively safe, easily administered and well tolerated medication which in about 60 per cent of anovulatory patients may be expected to induce more frequent and predictable ovulatory cycles. Better than one quarter of patients will become pregnant on therapy. The drug appears to be especially useful in women with medically uncomplicated oligo-ovulatory infertility with sufficient residual pituitary-ovarian activity to produce estrogen.

Followup of Clomid failures provides interesting data. Twenty-two Clomid failures (lack of pregnancy) subsequently received human menopausal gonadotropin therapy. Twelve became pregnant on HMG, five are currently in therapy and five failed despite HMG. HMG success was independent of previous responsiveness to Clomid as six patients became pregnant on HMG despite being totally anovulatory with Clomid. Interestingly, five wedge resections performed following unsuccessful Clomid have yielded pregnancy in two and regular spontaneous ovulations in the remainder.

HMG-HCG Therapy

It is recognized that this powerful new approach to treatment may not become generally available for some time. However, because it does achieve remarkable success rates in otherwise untreatable situations and is available on a referral basis at the Yale-New Haven Medical Center, the fundamentals of patient selection, mode of therapy and hazards will be reviewed.

Thirty patients have received HMG (Pergonal*)-HCG (APL*) in this clinic in the past 2 ½ years.[6] As in the Clomid series absent or diminished ovulation was the only discernible cause of infertility. Similarly, disease other than pituitary-ovarian dysfunction was excluded by preliminary workup. Three categories of patients have been treated.

1. primary or secondary amenorrhea without evidence of estrogen production (12 cases). The average duration of amenorrhea in this group was 6.3 years. Included were four primary amenorrheas and two lactational amenorrhea cases. Ten of these patients had no detectable urinary gonadotropin.
2. prolonged secondary amenorrhea but with evidence of estrogen production was noted in ten patients. The mean duration of amenorrhea was 3.2 years. A single case of primary amenorrhea was included.
3. eight patients displayed oligo-amenorrhea with intermenstrual irregularity of up to six months duration. Sporadic spontaneous ovulations were known to occur in this group.

Drug administration reflects the substitutional nature of this therapy. Follicle stimulation is achieved by eight to 14 days of continuous Pergonal (usually one ampoule I.M. q 12h) followed by an ovulating dose of 20,000 units HCG (5,000 u I.M. q 12h x 4 doses). The total dose of HMG and its duration is dictated by the degree of estrogen produced by the stimulated follicles. When cervical mucus changes (clarity, ferning, quantity, sperm survival) comparable to a normal cycle are achieved, HCG is added. Basal body temperature charts are kept during therapy.

Of the 30 patients treated, 26 ovulated and 18 became pregnant at least once on HMG therapy. A total of 84 treatment cycles were given of which 49 were ovulatory leading to 22 pregnancies. Five multiple births occurred (1 quad and 4 twin) and four pregnancies terminated in abortion.

The nature of the underlying pituitary ovarian disorder had a bearing on the effectiveness of the drug sequence. Of 12 patients in group (1) (anestrogenic amenorrhea) nine became pregnant on therapy. In group 2 (amenorrhea with estrogenicity) seven of ten patients achieved pregnancy. However, in only two of eight women with oligo-amenorrhea (group 3) was treatment productive of pregnancy though repeated apparent ovulation was achieved in all but one case. Regardless of category no pregnancy occurred on a total HMG dose of less than 1000 units. Ovulation usually occurred during APL treatment though rarely thermal shift was delayed 2-3 days.

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* Pergonal—brand of human menopausal urinary gonadotropin. Provided by Cutter Laboratories, Berkeley, California.

† APL—brand of human chorionic gonadotropin. Provided by Averst Laboratories, New York, New York.

In regard to side effects, despite the nature of the drug no pyrogenicity or allergic reactions were noted. However, the side effects of excessive ovarian stimulation (hormone excess, and acute enlargement) occurred frequently. Four women had ovarian enlargement greater than six cm. Three had associated intrauterine gestations. Aside from pelvic pressure and moderate pain, no alarming clinical situation arose. On the other hand almost all patients exhibited some degree of ovarian enlargement on therapy.

Two groups of patients failed on Pergonal therapy. One group did not ovulate despite high doses of HMG and only minimal increment in estrogen was noted. While these patients did not have ovarian failure, local responsiveness or ovum concentration was inadequate for appropriate response. In a second group of failures, represented entirely in the oligo-amenorrheic category, despite high frequency of ovulation, pregnancy rates were poor. Again local refractoriness to otherwise appropriate gonadotropin stimulation is possible. The local follicle principles influencing this receptivity are unknown.

Clearly the major problem facing further clinical trials is the reduction of excessive ovarian stimulation. While this matter is under intense study (the aspects of which are beyond the scope of this paper) no adequate monitoring system has evolved as of this writing. Solution of this difficulty is imperative, for the results of HMG-HCG therapy are so remarkable that eventual wide spread availability must occur.

Conclusions

In this report the effectiveness in one clinic of new medical therapies for ovulation induction are reviewed. At the moment Clomid has replaced cortisone derivative treatment in non-adrenal oriented infertility. However, the status of wedge resection is uncertain. Because neither of the drugs mentioned offers permanent reversal of anovulation and repeated therapy is required, wedge has this advantage. Nevertheless, the current program observed in our clinic places wedge resection as terminal therapy if Clomid or HMG-HCG therapy has failed. It is clear that failure with one does not rule out success with alternate therapy. However, use of any of these modalities in the single woman or in other gynecologic disorders seems unwarranted in the face of the availability of orally active materials of known mechanism of action.

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WHAT DOES MANKIND WANT?

. . . it begins to be apparent that mankind in all its restless striving and progress has no idea of what it really wants. Freud was right: our real desires are unconscious. It also begins to be apparent, that mankind, unconscious of its real desires and therefore unable to obtain satisfaction is hostile to life and ready to destroy itself. Freud was right in positing a death instinct, and the development of weapons of destruction makes our present dilemma plain: we either come to terms with our unconscious instincts and drives—with life and death, or else we surely die.—NORMAN O. BROWN.

Diagnosis And Treatment Of Male Infertility

Adnan Mroueh, M.D.

■ In the last two decades, understanding of the male factor in sterile marriages has assumed increasing importance. This is mainly due to our burgeoning knowledge of the physiology of human semen. The increasing use of artificial insemination by veterinarians as well as the general advances in reproductive physiology, have also contributed considerably to the trend of implicating the husband in infertility.

Criteria of semen evaluation are not uniform and the physician is often confronted with semen pictures where it cannot be decided whether conception is possible. Whereas generally the spermatozoal count has been used as the sole determinant of the fertility status of the individual, the qualitative aspects of the spermatozoa as well as the biochemical constituents in the seminal plasma should be considered to be of important prognostic significance. The lack of uniformity of semen evaluations in different institutions makes comparisons of data difficult. This is due to individual variations, methods of collection and days of abstinence. In cases where the initial examination casts doubt on fertility, it is important to repeat the semen evaluation. It must be remembered that semen analyses are merely anatomic descriptions of spermatozoal numbers and qualities and that these may or may not correlate with physiological integrity. Cases of functional spermatozoal infertility are known in other mammals.[1]

Several reports on semen evaluations in sterile marriages have appeared. Depending on criteria of normality, the incidence of unsatisfactory semen in infertile marriages ranges from 16 to 68 per cent. In this study, we have reviewed the semen evaluation in 500 infertile marriages and for comparison included the semen picture in 130 patients from the same clinic in whom conception was eventually achieved.

Materials And Methods

The semen specimens were obtained after a period of abstinence of five days. Patients were supplied with a clean, dry, wide-mouthed glass container and instructed to obtain the specimen by masturbation if possible, if not, then by interrupted intercourse. The specimens were brought to the clinic within three hours after ejaculation and examined immediately for volume, mucolysis, number of spermatozoa and motility by the method of Hotchkiss.[2] A smear for the sperm morphology as well as the presence of formed elements was obtained.

Out of a total of 500 patients, semen analyses are available on 309. The remaining 191 had no semen analysis because of the following reasons:

secondary infertility	47
impotence	5
"good" post-coital	5
"adequate" semen count	38
"poor" count	6
not done (either currently in the clinic or are lost to followup)	90
	——
	191

Of the 130 patients where conception was achieved, semen counts are available on 66. In the remaining patients no count was obtained for the following reasons:

secondary infertility	14
"adequate" count	16
not done	34

Results

Figure I shows the various semen characteristics in 309 cases of infertile marriage. It is noted from the figures, as the spermatozoal count falls, other defects in the semen increase. This is not surprising since the reaction of the testes to vari-

FIGURE I

Semen analysis in 300 cases of infertile marriage.

SPERMATOZOAL COUNT MILLIONS/CC.	NUMBER OF CASES	AVERAGE VOLUME IN CC.	PERCENT OF CASES WITH NORMAL MOTILITY (70% OR MORE)	PERCENT OF CASES WITH NORMAL MORPHOLOGY (80% OR MORE)
100+	71	3.11	64	72.0
80-99	28	3.25	50	75.0
60-79	26	3.10	57	65.2
40-59	45	3.14	52	61.3
20-39	48	3.34	35	40.0
1-19	49	3.72	9	21.0
Azospermia	33	2.50	—	—

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ous stressful agents is manifested by changes in cytology of the ejaculate followed by count depression. However this need not follow the same sequence, as cases of absent sperm motility despite normal morphology and count are known.

Figure II shows the graphic distribution of the spermatozoal counts in these infertile cases. If the arbitrary 60 million/cc is taken as the point of demarcation, then 65.8 per cent of the counts fall below this level, but if 20 million/cc is taken as the limit, then 26.6 per cent of the patients fall in this category.

McLeod and Hotchkiss[3] found that 49 per cent of semen specimens had spermatozoal counts below 60 million/cc in a group of 1500 sterile marriages. Keshin and Pinck[4] in a study of 135 cases in sterile marriage consider that 68 per cent of semen specimens were unsatisfactory, but they included abnormal morphology in their series.

Of great interest is the comparison of this group with a group where conception was achieved in the same clinic. It is seen that 6 per cent had counts below the 20 million/cc level and 37.6 per cent had counts below 60 million/cc level. (Fig. II) Of 200 men of known fertility, Hotchkiss et al reported 22 per cent had counts below 60 per cent million. It is obvious from[1] these results that one cannot arbitrarily forecast the fertility of any semen specimen provided spermatozoa are present. Nevertheless the chances of conception are considerably better when the spermatozoal count is over 100 million/cc. Whether this is dependent on the actual count or on the cytologic changes that accompany a higher count is a moot point. McLeod[6] found that the ease of conception is not different in fertile marriages when the count was over 20 million, provided the spermatozoal motility was comparable.

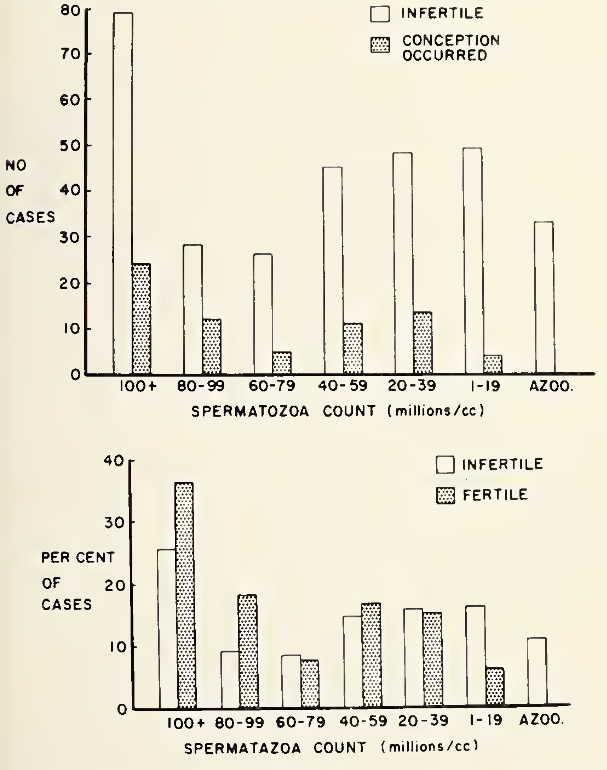

FIGURE II

Distribution of spermatozoal counts in infertility clinic patients.

Volume Of Ejaculate

The volume of the ejaculate depends on the period of continence as well as on the integrity of the accessory sexual apparatus, both anatomically and endocrinologically. The method of semen collection also seems to influence the volume.

As seen from Figure I, as the spermatozoal count falls, there is a gradual increase in semen volume. When the spermatozoal count is 100^+ millions/cc, the mean ejaculate volume is 3.11 cc, in contrast with a mean of 3.72 for oligospermic counts of 1-19 million spermatozoa/cc. Other workers have reported ejaculate volumes of 3.60, 3.2, 3.3 and 3.6 cc on various series of infertile men. Harvey and Jackson[7] found no correlation between sperm density and volume of ejaculate. However, in cases of azospermia, the mean volume of ejaculate was 2.5 cc. This figures differs significantly from both the oligospermic group as well as the overall mean of the infertile group. This could be ascribed to the fact that the azospermic group included cases of ductal obstruction as well as hypogonadism. Both conditions are known to contribute to decreased ejaculate volume. This figure compares with McLeod's[8] figure of 2.72 cc for azospermic males. Thus comparisons of various series is difficult because if the azospermic group is included, then the overall mean for infertile males tends to be lower. Johanson[9], however, reported the highest average of 3.6 cc in azospermic men.

In the group where conception was achieved, the mean ejaculate volume was 3.6 cc. McLeod[10] reported a volume of 3.38 for 1000 fertile men and Hotchkiss reported a volume of 3.12 for 200 fertile men. Kaufman[11] reports a volume of 3.0 cc in a group of 40 men and Farris found a volume of 4.3 cc. These series are not exactly comparable to men in our group, because all the above counts were on men of known fertility. The males in our group are partners in infertile marriages and may have decreased fertility potential which is not incompatible with occasional conception.

Mucolysis

The association of spermatozoal motility and mucolysis is apparent from table III a. It is noted that when the spermatozoal motility is 30 per cent or less then the mucolysis is poor in 46.5 per cent of cases. Whereas when the motility is 70 per cent and above, then the incidence of poor mucolysis is only 7.0 per cent. McLeod[8] feels that if the count is good then neither the motility nor the durability is seriously affected by poor semen mucolysis.

As seen from Figure 3b above, estimates of good semen mucolysis and consistency showed a linear relationship to the spermatozoal density.

Mechanisms concerned with semen coagulation-liquifaction are not fully understood. However, it is felt that a clotting enzyme produced by the prostate acts on a fibrinogen-like protein substance contributed by the seminal vesicles. Other stages include fibrinolysis by enzymes of prostatic origin and proteolysis leading to the formation of free amino acids and ammonia. Thus the association of azospermic semen with disturbances of mucolysis is not surprising since with azospermia the integrity of the male accessory glands may be compromised.

It is felt that semen consistency and viscosity interfere with fertility by impeding spermatozoal motility or by interference with spermatozoal transport in the female genital tract. Another mechanism postulated by Hotchkiss is that with a thick ejaculate spermatozoa must utilize their energy resources to move through the viscid medium and thus it is likely that their longevity is reduced.

Agglutination Of Spermatozoa

Semen specimens may contain clumps of agglutinated spermatozoa. The forward motility of these spermatozoa is lost. This clumping has been ascribed to the failure of reducton of an anti-agglutinin that coats the spermatozoal surface[13]. In this series clumping of spermatozoa was encountered more with semens that have a higher spermatozoal density. However, there was no difference in the incidence of agglutination between the infertile group and the patients in whom conception was achieved.

Leucocytes In Semen

Generally the occurrence of few white blood cells in the semen is not indicative of any inflammatory process in the testes or the accessory sexual apparatus. They are believed to be of epididymal origin and they perform phagocytic activity towards dead spermatózoa. Phadhe[15] found no correlation of leucocytes with the percentage of abnormal spermatozoa in the semen, or the motility of spermatozoa, nor were they dominant in cases of necrospermia. Our data, shown in Figure 4b,

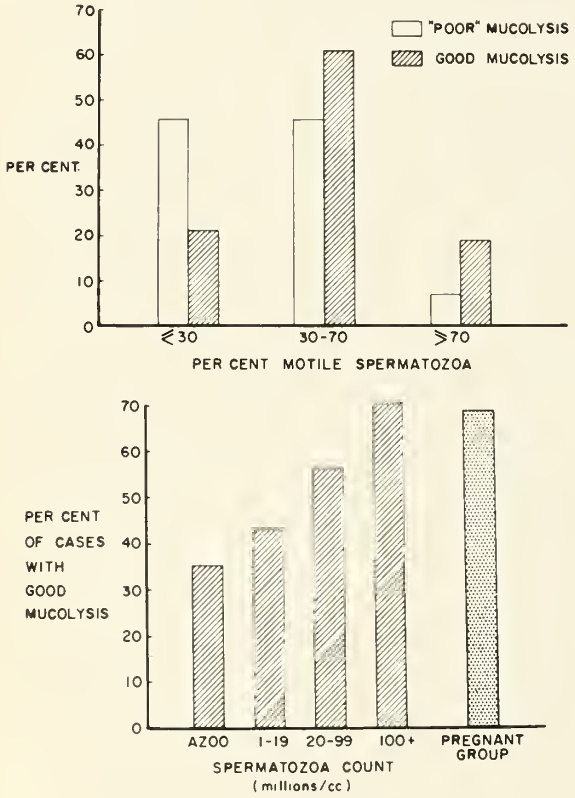

Figure IIIa and IIIb

Fig. IIIa—Variation of spermatozoal motility and degree of seminal mucolysis. Fig. IIIb—Variation of spermatozoal density and mucolysis.

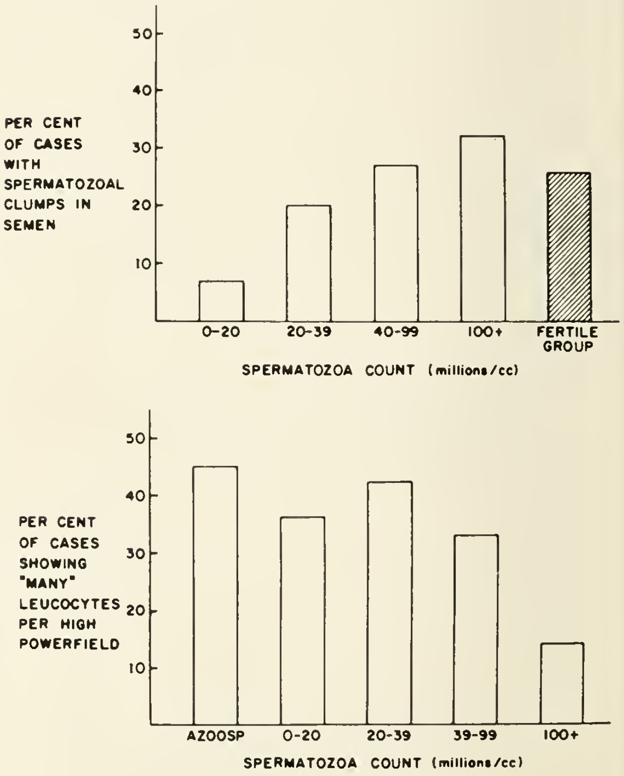

Figure IVa and IVb

Fig. IVa—Variation of spermatozoal density and the occurrence of spontaneous agglutination. Fig. IVb—Variation of spermatozoal density and the occurrence of leucocytes in semen.

indicates that leucocytes are more abundant in semen of lower spermatozoal density. This is at variance with the findings of Johansson who found no established relationship between number of leucocytes and sperm density.

Testicula Biopsy

Whenever the semen reveals any derangements, evaluation of the male must proceed diligently to rule out any systemic disease. Careful history especially regarding antecedent febrile episodes, intake of drugs or exposure to fumes or x-rays are especially significant. Details regarding psychic states are also of importance as testicular dysfunction is more common in individuals under stress.[15] A genito-urinary consultation is sought to rule out any local disease. The contribution of varicocele to male infertility is well established.[16]

In the above group of patients testicular biopsies were obtained on 52 males. The most frequent indications were in cases of azospermia where the size of the gonads was felt to be normal. In this type of patient ¾ will have a block in the accessory sexual apparatus. The second indication was to test various therapeutic modalities to correlate the response with a specific histologic pattern. The distribution of the various histo-pathologic lesions was as follows:

Germinal cell aplasia/hypoplasia	12
Arrest of spermatogenesis	15
Generalized hyalinization and fibrosis	8
Normal spermatogensis	17
Occulsion of vas shown by vasogram	4

The biopsy is helpful in revealing the nature of the insult to the testes. Because of their varying metabolic rates, the susceptibility of the germinal cells to noxious stimuli is variable. Generally, environmental insults such as drugs tend to interfere with stages of spermatogensis leading to exfoliation of immature spermatids into the ejaculate whereas genetic derangements lead to abnormal meiosis and thus the arrest of spermatogenesis is early at the level of the primary spermatocyte. The hybrid sterility seen in mules depends on the mechanical and physiological impediments to the pairing of maternal and paternal chromosomes at meiosis. [17] Thus the testicular biopsy reveals breakdown of spermatogenesis at the primary spermatocyte stage. In humans, genetic factors are reported to account for 11-20 per cent[18] of males with oligospermia.

Treatment

Over the past two years, several empirical therapeutic modalities were utilized in these patients. Because of the successful induction of ovulation in the female with urinary gonadotropic hormones, the possible use of these agents to initiate and maintain deficient spermatogenesis was explored. The effects of this treatment on steroid excretion and testicular function were evaluated by comparison with pre-treatment excretion values, sperm counts and testicular biopsies. It was found that while enhanced steroid excretion of testosterone conjugates, total estrogens and 11-deoxy-17-ketosteroids occured, no consistent beneficial effects on spermatogenesis were produced.[19]

Another group of infertile males were treated with Clomiphene Citrate* because the local antiestrogenic effect of this agent might inhibit concentrations of that steroid at the tubular level and estrogens are known to produce adverse effects on the tubular epithelium.[20] Here again, the results of this therapy were unsuccessful.

Although the adrenals and the gonads perform distinct physiological roles, there is close interdependence, the nature of which has not been fully elucidated. In the female, Jones[22] and her coworkers and Greenblatt[23] used cortisone successfully in cases of ovarian dysfunction accompanied by slight androgenic changes, postulating that they may represent mild variants of the adrenogenital syndrome. In the male, however, varying and inconsistent results were obtained. Gabrilove[24] and Perloff and Hadd[25] reported on 2 males with oligospermia with elevated 17-ketosteroids where adrenal-cortical steroid treatment was helpful.

In this clinic, males with a variety of azospermic or oligospermic conditions were treated with Prednisone for prolonged periods with no salutary effect.

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* Clomiphene Citrate—Courtesy of Wm. S. Merrell Co., Cincinnati, Ohio.

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IMPORTANT NOTICE !

TELEPHONE PRESCRIBING OF NARCOTICS STILL ILLEGAL

The 1967 General Assembly enacted legislation which would legalize the telephone prescribing of Class A narcotic drugs by physicians. However, the State's Attorney General has ruled that such legalization is applicable "only to the extent permitted by Federal Narcotics Laws." Since the Harrison Act (Federal Law) specifically *prohibits* the prescribing of Class A narcotic drugs by telephone, members of the Society are strongly urged not to do so. New Connecticut statutes notwithstanding, it's still illegal.

Immunologic Studies In Infertility

Lowell E. Olson, M.D.

▪ In 1955 Buxton and Southam reported an incidence of approximately 28 per cent "first degree infertility" (i.e., unexplained infertility) with an eventual pregnancy rate of approximately 44 per cent.[1] Hope, based on the statistical possibility of eventually conceiving, was all that could be offered these patients prior to the reports in 1964 by Franklin and Dukes[2,3] on antispermatozoal antibodies as a cause of infertility. Their work stimulated an attempt to determine whether or not immunological diagnostic techniques and modes of therapy could be routinely utilized in an infertility clinic.

Methods

The methods utilized in the immunological studies reported here were essentially those described by Franklin and Dukes. [2,3] Results were at first recorded by a written description of the agglutination phenomenon. However, after a period of experience it was possible to set up an arbitrary grading scale of values from 0 to 4 based on the number of sperm aggregations or clusters and the number of sperm per aggregation per high power microscopic field.

In January 1964, six months before applying immunological studies and therapy in a systematic manner to cases in the infertility clinic, immunological investigation of three groups of women was performed. Letters were sent out to those women who had been discharged from the infertility clinic during the previous two years as unexplained infertility problems after a complete infertility work-up and a minimum of three years infertility. These women were asked whether they would be interested in another investigation procedure. Those who replied in the affirmative, 27 in number, were designated as Group A. A second group of women, 46 in number, was obtained from the gynecology clinic. Each was between the ages of 24 and 40, had had a minimum of six viable deliveries, had not been pregnant within the past year, were not taking any medications, and had no evidence of an infectious process at the time of the study. This group was designated as Group B. A third group consisted of 31 unmarried, supposedly virginal, young women who volunteered for the study. These women were all between the ages of 18 and 23 years, had no menstrual abnormalities, were not taking any medications, and had no evidence of an infectious process at the time of the study. This group was designated as Group C.

Each woman in Group A provided a specimen of her husband's ejaculate obtained by the usual method less than 3 hours before the performance of the agglutination studies. In each case a semen analysis was performed. Blood specimens were obtained from each women in Groups A, B, and C. Agglutination studies were then performed as follows:

The blood serum of each woman in Group A was tested for antibody activity against her husband's semen specimen and against semen specimens from two to five other men. The blood serum of each women in Groups B and C was tested for antibody activity against a minimum of three semen specimens from conjugal partnetrs of the Group A women. The studies revealed that the degree of antibody activity had no specific relationship to whether or not the semen specimen was from a conjugal partner. A blood serum which exhibited apparent antibody activity against one semen specimen usually did so, to about the same degree, against all semen specimens with which it was tested.

Results

Table I summarizes the findings in the three groups of women. In addition to the 27 women originally designated as Group A, 50 more women meeting the criteria for this category were later studied and are included in the figures in Table I.

The results summarized in Table I are similar to those reported by Franklin and Dukes for comparable groups.[2,3]

Beginning July 1, 1964 those with demonstrated antibodies of the original 27 Group A women were instructed to restrict intercourse to the use of condoms or to abstain from intercourse except for one or two occasions at the time of expected ovulation as determined by history and basal body

TABLE I

INCIDENCE OF CIRCULATING SPERM-AGGLUTINATING ANTIBODIES

GROUP	A	B	C
Total number of patients	77	46	31
Number of patients with antibodies	47	11	7
Percentage of patients with antibodies	61	23.9	22.6

A. Patients with no demonstrable organic cause for infertility.

B. Patients of known fertility.

C. Patients of unknown fertility.

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temperature charts. This was advised on the premise that infrequent contact with the antigen or antigens in semen might result in a reduction of antibody. Between July 1, 1964 and July 1, 1965 another 50 women meeting the criteria of the Group A category were investigated and those who demonstrated antibody were started on the restricted intercourse regimen. In January 1966 after a follow-up period varying from 6 to 18 months during which time periodic checks were made of the antibody titers, the status of the 77 Group A women was reviewed.

Summary Of Follow-up Survey

77 —cases of unexplained infertility:
- 30 cases—negative for sperm-agglutinating antibodies (39 per cent)
- 47 cases—positive for sperm-agglutinating antibodies (61 per cent)
  - 15 positive cases—no follow-up.
  - 32 positive cases—minimum of 6 months follow-up.
    - 8 positive cases—no improvement in minimum of 6 months.
    - 24 positive cases—improved (75 per cent) of cases with follow-up).
      - 5 positive cases—improved to less than control (Group B) levels.
      - 19 positive cases—improved to control (Group B) levels.

Pregnancies

- 30 cases with negative antibody titers/5 pregnancies (16.6 per cent).
- 32 cases with positive antibody titers/9 pregnancies (28.1 per cent).
  - 24 cases with positive titers-improved/9 pregnancies (37.5 per cent).
    - 19 cases with positive titers-improved to control levels/9 pregnancies (42.1 per cent).

Outcome Of Pregnancies

Aborted	2 (22.2 per cent)
Delivered	7 (77.8 per cent)

Since the follow-up summary 2 more pregnancies have been reported. Thus, 52.6 per cent of the 19 cases with positive titers-improved to control levels have conceived.

In the 22 months between July 1, 1965 and May 1, 1967 another 161 women have been investigated for sperm-agglutinating antibodies. Sixty-seven have had positive antibody titers (41.5 per cent). Eight pregnancies have been reported in these patients.

The difference in the incidence of patients with positive antibody titers found in the studies prior to and subsequent to July 1, 1965 may be in part due to the fact that those patients in the earlier study had all had a known complete infertility investigation while many of the patients studied more recently have been referred patients and may not have been as completely evaluated. In several instances other significant infertility causes have been found to exist.

The pregnancies in the recently studied patients have yet to be evaluated in respect to length of time in the study, number of patients demonstrating improvement of the antibody titer and other pertinent factors.

Summary And Conclusions

In an attempt to determine the usefulness of antispermatozoal antibody investigation and treatment in cases of unexplained infertility, 77 women with no demonstrable organic cause for infertility were studied. An apparent antibody was found in 61 per cent of these patients. In the control groups 23.9 per cent of patients of known high fertility had positive antibody titers as did 22.5 per cent of patients of unknown fertility. Of the patients who followed the prescribed treatment 75 per cent achieved some reduction in antibody titers and 79 per cent of the patients who improved did so to the level of the highly fertile controls and 52.6 per cent have subsequently conceived.

The results suggest that there may be sperm-agglutinating antibody in the serum of some women. The incidence and degree of this antibody appears to be higher in women with unexplained infertility but may also be detected in the serum of highly fertile women. There may be no sharp demarcation between normal and abnormal levels of antibody titer but rather levels below which the antibody exerts minimal, if any, interference with conception and above which conception is unlikely to occur. The results of the study indicate that if the level of antibody activity is lowered the conception rate improves.

The reported pregnancy rate is not significantly higher than the eventual pregnancy rate reported by Buxton and Southam for first degree infertility.[1] However, of those cases where conception did occur the longest period of time between initiating the prescribed treatment and conception was 13 months. Perhaps treatment accelerates a lowering of the antibody which may have eventually occurred spontaneously and possibly in a few instances results in a lowering of antibody which would not have occurred spontaneously.

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Therapeutic Donor Insemination

Sophia J. Kleegman, M.D.

■ Our knowledge in many areas of human reproduction stems from the animal world. Artificial insemination has been employed by man for many centuries with animals, and animal husbandry has developed this method of breeding for improvement of the stock, as well as for profit. However, the first instance which took place in 1322 had a destructive objective when an Arab sheik secretly inseminated a pure strain of Arab mares belonging to his enemy with semen from inferior stallions.[19]

This was thought to be the earliest report of artificial insemination until a Talmudic document was found which antedates the Arabic tale by 1100 years. In this, the rabbis discuss what would the status be of a woman if she were accidentally and unknowingly inseminated by semen previously deposited in the bath water in which she bathed. The rabbis' opinion to this hypothetical question was that since the woman had become pregnant innocently and without intercourse, she could not be blamed for her condition.[24]

Although this is the earliest reference to human artificial insemination, the discussion was only academic and did not refer to intentional donor insemination. Thirteenth and eighteenth century rabbis continued discussing this hypothetical question. It is interesting that even then they expressed anxiety about the possible danger of the child later marrying a sibling unknowingly. They also had the same varied opinions as our own times as to the legitimacy of the child.

The first instance of human artificial insemination is credited to John Hunter of England, who in 1785 inseminated a woman with her husband's semen. In this country Marion Sims in 1866 performed 55 inseminations in six women, and again with their husband's semen. Only one became pregnant.[15] Throughout the 1800's there are reports especially from Europe, of husband artificial insemination. In this country Dr. Robert L. Dickinson, a pioneer in birth control, sex education, marriage counselling and other advanced practices in social and family mental health, had the courage to perform donor insemination in 1890, and on rare occasions after that. Although he did not publish this, he not only taught all the earliest practitioners in this therapy, but he is most responsible for its growing practice and acceptance. I was fortunate enough to share an office and a practice with him, and because of his encouragement, I have employed donor insemination, when indicated, since 1930.

Religious Aspects

Religion's teaching is that ethical conduct is determined by God and interpreted by His representatives, the clergy. One may therefore ask, "has the physician the right to discuss the religious aspects of this procedure when the authority rests in the clergy?"

When we seek for religious guidance we quickly discover that just as there is no one religion, so are the opinions held by various religious groups, and even within the same group, contradictory and confusing. In addition, during these past five decades, there has been considerable liberalization in the attitudes of many clergymen. In most groups belonging to the Protestant and Jewish faiths, no sectarian pronouncements have been made.

It is my policy to encourage all couples requesting donor insemination to discuss this with their spiritual advisers. This is particularly important for members of denominations which are opposed to this therapy. The Catholic Church, the Anglican Church and the Swedish Church still reject donor insemination.[25] Ironically Scandinavian physicians and social scientists approve of donor insemination on the principle that no woman who desires it should be denied motherhood because her husband cannot father her child. In Denmark the door has even been opened to unmarried women who request artificial insemination if they are considered exceptionally well qualified for motherhood. Most Protestant ministers take a neutral or permissive position and state that since their Church has made no sectarian pronouncements, each clergyman has to be guided by his own conscience.

Legal Aspects[13, 17, 48]

Religion has a powerful influence on law, and both influence and are influenced by custom and usage. Donor insemination, being in the field of sex, is in a particularly emotionally charged area. Change in mores passes through three phases. At first there is rigid rejection, then negation with diminished horror. This is followed by gradual

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curiosity, study, and evaluation, until we come to a slow but steady acceptance.

Social acceptance must be well established and widespread over a considerable period of time, with proof that it is beneficial to the individual, family and society before legal change occurs. All these steps are illustrated within our own time by slow and then rapidly increasing pace of liberalization of the laws governing birth control, divorce and recently abortion.

Donor insemination is following the same path. Fifty years ago there was very little usage and no established custom for this therapy.

Today there is increasing usage. One example of the indirect acceptance of this procedure is the fact that the Department of Health of the City of New York has specific regulations about donor insemination in Section 112 of the Sanitary Code, adopted July, 1947[41]. This governs the rules ascertaining the health of the donor, the use of RH negative donors for RH negative recipients, and the keeping of the records of such inseminations. The state of Oklahoma is the only one that has passed laws legitimizing the practice of artificial insemination using donor semen and has established the legitimacy of children born after such treatment.

Many physicians still question whether donor insemination is an ethical procedure[6,31]. No one's opinions are any better than his facts. In my experience, those most opposed to this therapy have had little or no experience with it. Whether or not it is ethical depends upon what is the effect on the individual, the family and the common good. The results depend upon the physician, the couple and the donor. Of these the physician is the most important. The first responsibility of all is towards the child. If this therapy results in the enrichment of the marriage, with children who are genetically well endowed, emotionally well loved, and who in turn will be an asset to the community, then in my opinion the therapy is ethical.

The physician is solely responsible for the two factors which determine the results—choice of couple and choice of donor. To choose wisely requires more than average ability and experience. It is essential that the physician have the training to understand the human personality and to evaluate the marriage relationship. Choice of couple and choice of donor rooted in such knowledge lead to excellent results.

Choice Of Couple[28]

The emotional criteria are of prime importance. The qualifications to be looked for are that each should be well adjusted and feel "well-married". This is not a means "to save our marriage". That is too much of a burden to place on any child. A shaky marriage is a definite contraindication to donor insemination.

They should have a true love of children, and individually and together, should prefer this procedure to adoption. Many a husband has said, "I prefer a donor baby because my wife is the woman I chose to be the mother of my children, and I would prefer to be the father of her children. Besides I too want to live through the experience of my wife carrying a child that I would feel to be my own." Other husbands say "perhaps this child will not be of my seed, but it will be of my heart." Almost all of them express greater security in the genetic endowment from a donor chosen by the physician compared with the unknown father of an adopted baby. Both must be in rapport in choosing this method of solving their problem.

My policy is to investigate the emotional qualifications before the medical ones. Adequate time is needed outside of regular office hours. Each is interviewed alone with assurance of inviolable privacy, and then together. The physician must be able to elicit how each one really feels. A conscientious husband who is ambivalent or even secretly opposed may feel "if I cannot give her a baby, I have no right to stand in her way of having her own." Counselling is then done to help him realize that his first obligation is to the child, that it will not add to their happiness, and that it may even hurt the marriage unless he too has his own need to have children and prefers this solution. Only in the separate interview can the physician elicit the emotional factors involved, and help each to acquire insight and perspective.

Occasionally the husband may confide that he came against his own desires, but is afraid to oppose his wife. This is a poor environment for a donor baby. Even worse is a domineering wife who is hostile and rejecting of her husband, in addition to being resentful of his infertility.

It is unwise to accept a couple for this procedure too soon after the husband's infertility has been discovered. He must be given time to recover from the severe shock that it is to almost every man. The degree to which each can make the adjustment to the situation and to the marriage is a measure of the emotional stability of each, and of the strength of the bond between them.

After adequate interview, if the physician is in doubt about the stability of the marriage, or any of the emotional qualifications, referring one or both to a psychiatrist for further exploration is a helpful procedure.

Medical Indications[28]

If the couple meet the emotional qualifications then the physician will evaluate the medical indications. These are:

1. When no sperm are found on two examinations and further investigation reveals the cause to be irremediable. In every instance of aspermia, an immediate post-ejaculatory urine specimen should be examined for sperm. The very rare instance of retrograde ejaculation of fertile sperm into the bladder will thereby not be missed, and the wife can then be inseminated with her husband's sperm[23,57].
2. When sperm are very few and/or abnormal, with clinical sterility of several years, and a fair trial with intra-uterine insemination of a split ejaculate has been ineffective.
3. When Rh incompatibility has already resulted in erythroblastotic infant (s), and the couple request insemination of the wife with an Rh neg. donor.
4. When the husband's family history of genetic disease seriously threatens the potential normalcy of his own children.
5. When previous children of their own manifested genetic disease (Tay Sachs, Von Gierke's).
6. When both husband and wife have demonstrably reduced fertility, medical help has been unsuccessful, and the couple request the physician to obtain highly fertile sperm to improve the wife's chances of having a baby. This group requires particularly good judgment. We have taken this measure only occasionally when the wife's age constitutes an additional threat to her potential fertility.

Contraindications

1. If there are any medical contraindications to pregnancy.
2. If they do not meet the standards presented under emotional qualifications. The physician cannot afford to compromise in this area.
3. If the wife has a history of serious genetic disease in her family. Most physicians would need consultation with a geneticist.
4. If full knowledge and unqualified consent by each partner is lacking.
5. If the couple have informed their friends and relatives of their plans for donor insemination.
6. If the couple want to choose their own donor, a friend or relative[15].
7. If the couple has just learned of the husband's sterility, and this knowledge has not yet had the chance to demonstrate its influence on the couple and on their relationship.
8. If during the counselling sessions between the physician and couple, doubts have been raised about any phase of it, either in the physician, or in the couple.

The motivation on the part of either mate to request donor insemination without the knowledge or consent of the other partner may be altruistic. Often the request is made because "I don't want to hurt him, and if he knows he is sterile, he would feel crushed." Without exception, this request has been refused. It is unwise and unethical to carry out this procedure without the knowledge, emotional acceptance and signed consent of both partners. A person too immature to come to terms with reality, or a marriage which could not survive truth presents a contraindication to this therapy.

In order to weed out all but those who are most anxious for this help, our policy is to encourage them to stop if either show any inclination to do so. No set sum is collected to cover a specific time or treatment. Fees are charged only for each treatment as given, and in general, fees are lower than for other medical services in proportion to the amount of time and trouble involved. This makes it easier for couples to stop treatment any time, even shortly after a start has been made. They are reminded regularly that it is a gamble, that it is "all or nothing". The possibility of disappointment is stressed and emphasized.

Choice Of Donor[28]

This is almost as important as choice of couple, and again this is solely the physician's responsibility. I have always refused the request of the occasional couple who preferred to choose a friend or relative as the donor. There is too great a risk that this would create serious emotional problems later on. For appropriate choice of donors, the physician needs resources from which to select a number of highly fertile men, of superior genetic endowment and intelligence, with varied ethnic and religious background[40]. Complete anonymity between donor and couple is maintained strictly. These requirements cannot be met in a small community.

Recruiting a suitable group of donors even in a large metropolitan city is an arduous task for the individual physician. We have the opportunity and the responsibility for eugenics to rule[39]. The majority of our donors come from the intern and resident staffs of our local hospitals. They are more easily available on short notice than medical students. Married men are accepted only if the wife is aware of and is sympathetic with the program. We do not accept a husband of an infertile wife since this might accentuate her sense of inadequacy and frustration. Frequently the husband of a wife whose indication for donor insemination is Rh incompatibility offers to be a donor because "this has given our family so much happiness, I would like to help out some other family". If suitable, they are accepted. Some of our donors are students in one of our colleges of music and are chosen when the recipient couple is musical.

Careful matching of physical appearance is done, and if the coloring of the husband and wife differ, we are apt to choose the husband's coloring. When the baby is born, and later on, it delights us and the couple when the relatives comment, "spittin' image of the old man". Amazingly often, the child is. Religions are matched except that Christian donors are chosen for Jewish couples who had a child with Tay Sachs syndrome.

When potential donors are interviewed, careful inquiry is made of the family history. Genetic diseases and tendencies are inquired for carefully. We are of course entirely dependent on the donor's honesty. It is reassuring that with the group from which we choose, once the importance of their truthfulness is explained, many rule themselves out by reporting unfavorable family history. In addition their sperm has to be in the highest level of fertility as evaluated by detailed semen analysis and by the subsequent results obtained.

The physician has the obligation to protect the donor's emotional needs as well. His feelings about being a donor should be explored with him, particularly the possibilities of this being a matter of regret in the future. If the donor is rejected because his sperm count is lower than our standards for donors, or some of the other sperm findings indicate fertility which is not expecially high, we assure him that our not accepting him as a donor does not mean that he will be unable to have children when he wants to. Many applicants whom we have refused, subsequently have no fertility problem. If occasionally we find that the prospective donor has a severe infertility problem himself, we are truthful with him, give him whatever emotional support possible, and guide him towards medical help.

If accepted, the donor is then instructed in the delivery of the semen. He is told to wash his hands before obtaining his specimen by masturbation, and to ejaculate into a cool, sterile glass container. The specimen, properly wrapped and addressed to our office is then immediately given to a taxi man or special messenger service. In this way, donor and recipient never meet. The semen usually arrives at the office within an hour after it is produced. The donor is paid $20. to $25. per specimen.

Procedure

If the emotional and medical qualifications are met, the couple signs a consent sheet. (Fig. I)[28] This is kept in a safety vault and is the only legal protection we have for the child as well as for us. Its main value is the insurance that should there be marital conflict leading to legal action later on, the husband or wife cannot claim that the donor insemination was done without knowledge and consent on the part of each. The couple is advised not to share their plans with any friend or relative, and to keep no memo among their papers about this. Legal adoption of the child by the husband is not advised.

I, the undersigned, co-signer with my wife, Mrs. *Mary Smith,* hereby request Dr. *Kleegman* to inseminate my wife with the sperm of a foreign donor for the purpose of making her pregnant.

The choice of the donor is to be left entirely to the discretion of Dr. *Kleegman.* We shall not hold Dr. *Kleegman* or her associated physicians responsible for any untoward results as a possible outcome of this procedure.

I also declare that should my wife bear any child or children as the result of such insemination (s), such child or children shall be as my own before all men, and shall be my legal heir (s).

Signed *John Smith*
Husband

Mary Smith
Wife

Date

Witness (Secretary)

Witness (Physician)

FIGURE I

Consent sheet signed by couples in this series. (From Kleegman, S. J.: Therapeutic Donor Insemination, Fertility and Sterility, 5: 7, 1954.)

If this measure is necessary to protect the child, then the couple is emotionally unsuitable. It is to the credit of the medical profession that with many and increasing thousands of donor babies in this country, there have been only a few couples who exposed their child to public display of his parentage, in the course of taking their marital conflict into court. As more protective laws will be passed for the children of donor insemination all children will be protected against such trauma.

Management Of Treatment

If past history and pelvic findings indicate that the fertility is normal, no fertility tests are done. It seems pointless to subject a woman to an infertility diagnostic study when she has not had the opportunity to demonstrate her fertility. This policy is particularly supported since, of those women who do conceive, one third do so after treatment in the first cycle.

Choice Of Day[14, 34]

That depends upon how regular her menstrual cycles are. She is given a basal temperature chart with detailed instructions how to keep it[58]. Subjective symptoms of ovulation, ovulatory mucus and ovulatory discomfort, "mittelschmerz", are asked for. If she is aware of them, the choice of day is simple. If she has none, they are nevertheless described to her in detail, and she is asked to watch for them, and record them on her temperature chart whenever they occur[26, 45]. Fifty per cent of women have or can be taught to recognize some subjective signs of ovulation. When she has a complete cycle recorded, we then have a better idea how to chose the day, or instruct her how to choose it. We do not arbitrarily set up three treatments every two days during the mid-cycle, which is the custom of some physicians. We try to pinpoint the day closely enough to give her one appointment. If two days later, she shows no signs of having ovulated, she will then call and we arrange a second appointment that day. Only occasionally do we have to give a third treatment in the same cycle. If no pregnancy occurs after treatment in two cycles, then we do a tubal insufflation with CO_2. If she has not conceived after treatment for six cycles, then she too has a fertility problem, since of the women who conceive, 90 per cent do so within 1-6 cycles. She is then advised to have a diagnostic study for infertility before continuing further[35].

If the woman's cycles are ovulatory but irregular —30 to 40 + days, she is taught the "self-stretch" test[34]. This is a coined word for teaching her how to aspirate her vaginal secretions starting 3—4 days before her first expected day of ovulation, and continuing daily until about two days after ovulation. She is taught how to look for the changes in the aspirated vaginal secretions. Quantity of mucus, change in appearance from white to clear, and particularly the height to which the mucus can be stretched are all noted. This has made it possible for us to treat women successfully with cycles which vary from 40—80 days. We had one woman who ovulated and became pregnant on day 71 in her cycle. The physical changes in the aspirated mucus[9,10,44] and the recognition of ovulatory discomfort when present[55], will save many useless and needless inseminations. For this kind of management, one must be able to alert donors and they must be able to respond to a call on the day they are needed. This is much more burdensome to the physician than setting up three treatments in advance, but it does reduce the number of ineffective treatments given too long before ovulation, or too late after ovulation. In our series between 58 per cent—60 per cent of those who conceive had only one insemination in the cycle of conception[28]. An additional 32 per cent had two inseminations in the successful cycle.

"Will you mix my husband's semen with the donor's?" is frequently asked, whether or not the husband has any sperm at all. For the first fifteen years, and if the husband did have some sperm, the husband would come with his wife, produce a specimen, which I would then instill into the vagina directly after injecting the donor's semen. If the husband had no sperm, the couple would be told that there were none to mix. This type of "mixing" was a hardship on the husband for several reasons, especially since many of the couples came from a distance. Therefore for the past twenty years my answer to this question is— "The best way to mix sperm is for you to have intercourse the night of the treatment day. It is a more natural way of mixing and helps to move the sperm along". This has satisfied the couples and often the husbands feel they have an active participation in helping towards a successful outcome.

Technique Of Insemination

The woman is placed on the table and pelvic examination is done. An unlubricated, sterile speculum is inserted and the cervical os is exposed in good light. The endocervical secretion is aspirated with a glass pipette attached to a bulb for evaluating the presence of the ovulatory characteristics of cervical mucus, quantity, appearance, spinnbarkeit, cellular content and fern.

The foot of the table is then elevated so that the pelvis is tilted at an angle of 45°. The semen is aspirated into a cold, dry, sterile syringe attached to a cannula.* Two drops are taken for microscopic examination for number of sperm, their motility, and number of leukocytes. The tip of the cannula is placed just within the external os, and the semen is instilled slowly.[35] Most of the semen flows back into the vault of the vagina. The speculum is then withdrawn slowly so that none of the semen is withdrawn with the posterior blade. Because of the tilt of the pelvis, this leaves the external os submerged in the seminal pool. The foot of the table is then lifted, and she is left with her pelvis elevated and her body stretched out full length comfortably for 20-30 minutes. With the years, several other variations of technic have been tried. For a time I used the cervicap as suggested by Whitelaw[61] but the results were not improved thereby. The study done by Sobrero and MacLeod[54] which shows the almost immediate insemination of the cervical canal following intercourse may be the reason. Allowing the patient to lie on the table for at least 20 minutes does improve the percentage of conceptions. Tilting the pelvis up projects the cervix directly into the pool of semen. Before the woman gets off the table a lamb's wool tampon is inserted into the middle third of the vaginal canal to save the annoyance of the drip, and the tampon does not absorb the semen. It is interesting to note that active sperm are found in the cervical secretion 2–3 days after insemination, and occasionally sperm of good motility are found as many as five days after insemination. To what degree they have the capacity to fertilize is difficult to say.

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* The Kleegman cannula is manufactured by J. Marco and Son, 601 Dow Avenue, Oakhurst, N. J.

Invariably, the couples who return for more children want the same donor "because this baby is so wonderful". The answer is, "we promise you only that the donor will be superior genetically, that he will be of similar religion and national origin, and the physical appearance will be matched carefully. All else of the child's personality depends upon what you, his parents, provide for him in his environment."

How should the birth certificate be signed? Those who treat the woman and then deliver her do not hesitate to record the husband as the child's father, and anonymity is carefully maintained[15,19,20,45]. Since many of our patients come from a distance, they are advised not to disclose to their local obstetrician the history of the onset of the pregnancy since it has no bearing on the obstetric care. Therefore as far as the child's world is concerned, he is the child of the couple. Medical ethics requires that the protection of the well being of the child and of the family requires the highest priority.

In the report on donor insemination given in 1953[28], the possibility of a frozen semen bank was discussed with the possibility that each semen specimen be so carefully and comprehensively recorded that the needs of each couple be met on an individual basis. I did not know that a start had already been made, for in the same year four normal babies were reported as the result of using frozen semen obtained from donors[4].

There are now several centers which maintain frozen semen banks, and the freezing process has been considerably improved. Normal babies have been reported by several workers in this field just in the past few years[3,5,16,43,47,50,51,62]. Although the percentage of motile sperm, even when good sperm are frozen, is less than in a fresh specimen, and the percentage of pregnancies lower[3], this technique will make good frozen semen available anywhere in the country. Some of these babies were conceived from frozen semen flown a considerable distance to the physicians[51].

As an example of the increasing acceptance of donor insemination, in my own practice, four couples were treated with donor insemination from 1930–1934; 10 from 1935–1939; 181 from 1945–1959 (some of these were repeaters). With this increasing acceptance by our society, and the increased legal protection which the children and mothers will have in the near future, and with the availability of frozen semen to any geographic area, there is now even greater need that the physician and the couple should have the protection of better supervision and direction.

Undoubtedly most of the frozen semen banks will be housed in medical centers, so that the choice of donor will have the advantage of expert supervision. On the other hand, there are now available semen banks small enough to fit into a private office. Few physicians have the psychological training to choose the couple with adequate protection not only to the child, but to the couple's emotional needs as well. Therefore there should be resources established in every medical center so that physicans can refer couples for counselling, both as to donor insemination and genetic counselling in order to safeguard the potential great good of this therapy[51].

The terminology varies depending on the author. However the most frequent terms used are A.I.D.—artificial insemination donor, and A.I.H.—artificial insemination husband. I personally prefer to diffentiate between the term "artificial insemination," which has long been used in animal husbandry for financial profit, and insemination of the wife of an infertile husband for the cure of that couple's sterility. In addition, artificial insemination in the human has been the subject at times of lurid sensationalism. For these reasons, and because of the negative association with the word "artificial", the term *"therapeutic"*[51] donor or husband insemination is recommended depending on the source of the sperm.

Results

It is interesting that with the years the pregnancy rate has not risen. This is probably because from my earliest years of practice Dr. Robert L. Dickinson, that master clinician, taught me the details of detection of ovulation[10,11]. Also, the donors chosen were always restricted to the highest potential of fertility. Potter[46] in analyzing seven authors, series [28,52] stated that the methods of computing statistics were not accurate. Our method is to count anyone who has received only one insemination without becoming pregnant as a failure, since so many of our patients, who become pregnant after only one insemination are counted as a success. On that basis, at last count taken in 1965, we have about 300 babies, with two sets of twins. The percentage of women who become pregnant after 1–6 cycles was 68 per cent.

The follow-up of the children and families has been particularly rewarding. With two exceptions these children are as a group more outstanding than are the children of infertile parents who had their own, and the group whose parents had no fertility problem at all. I believe the reason is that these children were more wanted and more cherished.

With the help of yearly Christmas cards, the follow-up has been particularly good. There has been one divorce when the child was 4½ years old, but the father loves his child "more than anyone else in the world" and has remained a devoted and generous father for 24 years. The mother has been wise enough to support this good relationship.

World War II trapped one mother and her child in the Near East. After six years of this enforced separation she preferred to remain there with her family. One child, now 20 years old, is having serious emotional difficulties with her mother relationship. The mother is one woman whose emotional instability I missed until the end of the visit when I had given her the first treatment and resolved then to go no further. However she became pregnant. Her marriage has been progressively deteriorating. Nevertheless the husband has remained because of his devotion to the child.

To my knowledge, four of the children had emotional problems severe enough to require some psychological, and in one instance, psychiatric help. The emotional problems were unrelated to the donor insemination. All these children were helped and are doing well. The intellectual and achievement level of these children is a tribute in part to the donors.

Complications

All occurred in the group reported in 1954 (28). We have not had any since. Two women were infested with trichomonads, although the parasites were not recognized in the semen. Two women developed streptococcal pelvic infections 7 and 12 days after insemination from a semen which was split between them. One did not get pregnant that cycle, and she developed an acute salpingitis with pelvic peritonitis. She responded well to penicillin. Fortunately she made a prompt and complete recovery since she conceived later with donor insemination.

The other woman conceived in that cycle, had a low grade temperature for three days, moderate abdominal pain, and responded quickly to antibiotics. The rest of her pregnancy was uneventful, with a normal delivery and puerperium, and full term normal child. She subsequently had two more children with the help of donor insemination.

Six couples with one or two donor babies subsequently had one child of their own, and one couple had two. Of these, semen examination done shortly after the onset of pregnancy showed no improvement of the sperm in four, and significant improvement in one. One was not rechecked. In one couple, the husband was aspermic and testicular biopsy showed marked fibrosis before the wife was treated. She then had two babies following donor insemination. When she had her third child without any help other than with her husband, she was entirely co-operative in asking her husband to come and have his semen rechecked. Not a single sperm could be found. The report I gave him was "You're just lucky".

Four women whom we treated unsuccessfully with donor inseminations for one to six cycles subsequently became pregnant with their husbands and had full term babies. One of these husband's semen showed notable improvement and the other three were just as poor. One woman, in between two donor babies, became pregnant with her husband, and aborted spontaneously in the second month of gestation. Her husband's semen was extremely poor.

Three couples who came for donor insemination because the semen was very poor, and the period of infertility was four or more years were given a trial with intrauterine insemination of a split ejaculate[27]. The split ejaculate specimen contained an adequate count—60 million or more, and they became pregnant within 1—3 months. Many other couples with semen in equally poor levels did not become pregnant with this trial with their husband's semen and subsequently did become pregnant with donor insemination.

It is comforting to know that in these couples who had children of their own after the donor babies, the parent-child relationship was not disturbed in any way. Interestingly enough, each of these fathers said "I'm sure it is because of the happiness brought by our first children that we were able to have this one together." This illustrates the importance of careful choice of couple based upon their emotional qualifications.

Preventive Measures[33]

It is amazing how few of these husbands knew of their infertility before marriage. Even the group with cryptorchidism who did not have surgery until after puberty were, with few exceptions, given no hint that they might be sterile. Only a few knew of their sterility and informed their prospective wives before the wedding. These couples married with the plan to have donor insemination.

Even today, too many instances of crytorchidism are not treated early enough[1,7]. Apparently more education of physicians is needed so that they include palpation of the scrotum routinely as part of their general examination.

Since varicoceles may reduce the fertility of the sperm, varicocelectomy is indicated for husbands who show evidence of impaired fertility [1,8,38]. Annual examination of the sperm should be done on any man with a varicocele even before marriage to watch for any noticeable damage to the sperm.

Prevention of venereal disease in both sexes is an important measure. Although the incidence in private practice is much lower than in clinic patients, there is a rising incidence among the general population, particularly in the younger groups. Educational and therapeutic programs need to be carried out more vigorously. The medical profession has the particular responsibility to make sure that each infection is reported to the local health department so that the chain of infection may be traced to its source.

Hopefully, some protective immunization against mumps will be developed and thereby reduce the small percentage of males rendered infertile by mumps orchiditis.

A widespread program of education for sex, marriage, and parenthood would not only lead to more harmonious home life, but would also protect and promote fertility[12,32,36]. For example, it would reduce the incidence of impotence and frigidity[29,30,53]. To an increasing degree, medical educators are beginning to meet their responsibility by taking "the leading role in initiating a national program for educating the medical profession in family life aspects of patient care"[37]. The pace of this increase, hopefully, will be quickened.

Summary

Therapeutic donor insemination helps the wife of the sterile or seriously infertile man to achieve her emotional and biological fulfillment as a mother. It is a therapy in which the medical aspects are subservient to the emotional, religious, social and legal thinking.

There is a rapidly growing acceptance of this therapy, particularly in the past fifteen years, which has affected a change in mores of sufficient degree so that for the first time, Oklahoma passed a law legalizing donor insemination and protecting the legitimacy and inheritance rights of the child, as well as the marital integrity of the couple.

Experience of one physician is presented covering a span of 37 years, during which time about 300 babies have been born as a result of this therapy. Follow up of about half of these babies over a period of years, has proven that with experience and careful choice of couple and of donor, therapeutic donor insemination results in superior children who are of benefit to their families and to their communities. The complications and untoward results are fewer than in comparable groups of children conceived naturally between husbands and wives.

Frozen semen banks have been the source of a small number of children. This group will undoubtedly increase in the future, since this will make donor semen available to couples in any area of this and other countries. This makes it necessary that this field be supervised by qualified experts in medical centers who will take the responsibility for advising the physicians and the couples. This supervision should also be extended to the assembling of suitable donors with superior eugenic and personal attributes.

Little is known about many aspects of male sterility and infertility[1,22]. Some preventive aspects are presented.

Physicians and medical organizations interested in this field need to further the start already made to pass laws to protect the children resulting from this treatment and to protect the marital status of their mothers.

Therapeutic donor insemination is necessary and good if carried out within the framework herein presented. The children are superior, the families involved are enriched and therefore contribute to the good of the community.

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Agency Adoption Practices In Connecticut

Nathan E. Sklar, A.C.S.W.

▪ Obstetricians in Connecticut should feel comfortable in referring couples to adoption agencies. Long waiting lists, endless interviews and "ideal matching" of child to the parents are passe.

Agencies are publicizing the number of children placed for adoption. Public forums, and newspaper articles are being utilized constantly by agency staff to seek out possible applicants. This is in sharp contrast to the situation prevalent before the passage of Public Act 203 at the 1957 Legislative Session, which virtually eradicated the independent placement of illegitimate or unwanted children by third parties.

No Probate Court may accept an application for adoption unless: (1) the child to be adopted has been placed in the adoptive home by the Commissioner of Welfare or by an agency licensed by the Commission; (2) the child is to be adopted by a close relative, namely, a step-parent, sister, brother, aunt, uncle or grandparent; (3) the child is received by the proposed adopting parent from an authorized agency outside the state with written consent of the State Welfare Commissioner of Connecticut.

Under this act it is possible for the mother to surrender her child to an authorized agency by deposition, without a court hearing. This procedure allows for early placement of the child with the adopting couple. The Catholic Charities of the Diocese of Bridgeport normally places infants at the sixth or eighth week of age, "except if delays occur because of medical care or out of consideration for the mother's delay in reaching a decision." Woodfield, a maternity home in Bridgeport, states "almost all . . . placements are infants under three months, consistent with Child Welfare League of American standards."

It is possible to place children with families of a religion different than that of the mother, providing consent is given to the agency. However, every effort is made to find an adoptive home compatible with the religion of the mother.

Applicants now are not automatically rejected by agencies if there are no infertility findings. For example, the Catholic Charities, Diocese of Norwich, as a matter of policy noted in a letter, "in keeping with good social work practices, we do not reject applications where no known medical reason accounts for childlessness". Another approach to the problem of infertility utilized by the Children's Services of Connecticut, Inc., based in Hartford but serving many sections of the State, is to request the applicants to file a medical statement regarding the cause of infertility. "This does not mean that there has to be proof of infertility but we want verification that a family has done what they can to have natural children."

In a newspaper article, the Director of the Jewish Family and Children's Service of New Haven made reference to second and third adoption placements having been made with a family who have had other children of their own or through adoption. The Family and Children's Services, Fairfield County, in a policy statement approved by the Board of Directors, January 18, 1965, provides that ". . . couples having one child and unable to have a second are most welcome to apply. The agency gives special priority to applications for a second child by parents whose first child was adopted through it, believing that families prosper best where there is more than one child."

Policies on length of marriage and age have come in for a drastic overhaul. Jewish Social Service of Hartford, for example, has no defined age limitations for applicants but requires that the couple should be married at least three years. Other agencies vary on marriage requirements with the maximum being at least five years. There is usually a cut-off on eligibility if the husband is over forty-five years of age. Leeway is given on age if the particular child is handicapped or an older child is being considered for placement.

Fees are related to the economic situation of the adoptive parents. The maximum fee is fifteen hundred dollars based on an annual income of over fifteen thousand dollars. Some agencies waive fees if indicated. Based on a survey of agencies the range of fees, including court costs, would be two hundred and fifty dollars up to fifteen hundred. Again, the policies stress that every couple is given consideration of their particular circumstances to facilitate placement. One Connecticut agency, written up in the Wall Street Journal, actually subsidized low income families who took

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more than one child. This concept derives from the theory that difficult to place children because of racial factors should be given every opportunity to become part of a family rather than suffer innumerable short term foster home placements.

Physicians who have couples capable and willing to accept physically handicapped children, or siblings who must be kept together, or children of minority groups, should be referred to the Adoption Resource Exchange, of the State Welfare Department located in the State Office Building, Hartford, Connecticut. Mrs. Marie Corder, supervisor of the Exchange, in the 1966 annual report, cites that thirty-four couples accepted thirty-six children during the year. Of the group two had severe physical handicaps, two had mild physical handicaps, and two had severe emotional problems. The Exchange serves as a clearing house for all child placing agencies in the State. Of five hundred twelve children registered from May 1, 1960 through June 30, 1965, two hundred thirty four were adopted.

The State Welfare Department succeeded in effecting sixty adoptions in 1965-1966. State workers assist Connecticut couples who may be adopting children from out of state agencies by completing studies for the court in cooperation with authorized agencies outside of the state.

Between the State Welfare Department and Connecticut private social agencies a total of eight hundred and forty-five children were legally adopted for the year 1965-1966. The median age at time of placement was 2.1 months by private voluntary agencies and 25.4 months for the State agency. The pronounced difference is due to mitigating legal factors in securing termination of parental rights preliminary to adoption.

This information indicates that social agencies are eager to cooperate with their clientele in providing a positive experience. From time to time popular articles decry the inflexibility and restrictive policies of social agencies which make it virtually impossible to adopt a child. Our Connecticut experience proves to be otherwise.

Obstetricians who are daily confronted with patients whom they feel should be referred to social agencies should not hesitate to do so. When discussing referrals it would be wise to regard social agency personnel as consultants who are professionally qualified individuals available to assist the patients to achieve desired goals. It is understandable that physicians and patients who have had no previous experience with social agencies may be apprehensive about what is to be expected once the initial appointment is agreed to. Patients should be apprised of the changes that have taken place in Connecticut Social Agencies, especially the myth of being mired in red tape. The old stereotype of a busybody social worker should be laid to rest as standards for social workers have improved to the point where most private agencies require their staff to have a masters' degree from an accredited school of social work.

Agencies, public and private, require medical information on the referred couples. The information is confidential. The couple will sign a release for the physician to submit appropriate medical data on the agency form. One part would be a general physical and the other on infertility. All agencies have medical consultants who devise the forms. If questions do arise on the information submitted the referring physician will be consulted. The consultation usually would relate to the question of longevity of a potential parent because of heart disease or other positive findings noted in the examination. However, the primary concern of the agency is to ascertain that couples have explored their inability to conceive. Agencies utilize the medical data ". . . not prohibitively, but rather to better understand their clients and help them reach the most sound decision".

Regarding the agency study of the applicants, there are no absolute rules that qualify or disqualify. An honest attempt is made to assess all factors, health, length of marriage, age, capacity to love and guide a child to develop his potential. Office interviews are conducted along with home visits so both the agency and the couple have a better understanding of the entire process. Usually, the agency after accepting the couple is able to place a child for adoption from within two months to a year. Personal references are interviewed with the consent of the couple. One agency has established a procedure for a group orientation interview where there is an opportunity to learn firsthand of the agency program. Following discussion, the couples are given application and medical forms. As soon as the forms are received the adoptive study commences.

United States Children's Bureau statistics indicate that there are over 1.5 million adopted children in the United States with the number increasing yearly. For example, 121,000 in 1962; 127,000 in 1963; and 135,000 for 1965. Social agencies accounted for two-thirds of the adoptions which reflects a change from the former ratio favoring independent placements.

A perennial problem is the placement of non-white children. The Child Welfare League of America reports approximately ten percent of all children who were adopted were non-whites. This includes two hundred and fifty Indian children placed with Caucasian families through member agencies of the League. Other agencies are recruiting couples or parents with children to adopt babies of mixed origin with some success. International Social Service has effected 1600 interracial placements with American families. In Connecticut, the Connecticut Child Welfare Association, Inc., The Connecticut Resource Exchange and private agencies are constantly publicizing the good results accruing from interracial placements.

Inherent in any discussion of adoption is the concern for the unwed mother. The National Center for Health Statistics of the U. S. Department of Health, Education and Welfare estimates 275,700 illegitimate live births occurred in 1964. A Department of Health Report, City of New Haven, dated March 10, 1966 showed a four-fold increase in illegitimacy in the last ten years with sixty-five percent of the babies being born to girls under age twenty-four.

These figures warrant serious attention not only by social agencies but by the medical profession as well. Philip M. Sarrel, M.D., Department of Obstetrics and Gynecology, Yale University School of Medicine, studied Yale-New Haven Hospital records of 100 teenage girls who had become unwed mothers. Of this group who delivered their first baby between January 1, 1959 and December 30, 1960, the study revealed that in five years the girls delivered two hundred and forty more babies out of wedlock. There were also nine abortions.

A special clinic has been established at the Yale-New Haven Medical Center for unwed mothers through the age of seventeen. To assure continuity of care a social worker is assigned to follow these young patients on an individual and group basis from point of clinic registration through six months post-partum. In this period the patient is seen by one obstetrician. Due to the concern of the clinic staff a day center has been established by the New Haven School system which offers courses tailored to meet the needs of the girls. Reentry into the regular school system is eased considerably through this approach. Where formerly the girls lost interest in homebound instruction or simply failed to request school assistance during confinement, they are now accepting the program offered with a positive attitude.

Through group and individual counseling the social worker involves the obstetrician who discusses family planning, labor, delivery, pediatric care and the post-partum check. As Dr. Sarrel states, "the obstetrician's role is central to the program." He meets regularly with social worker, clinic nurse and other personnel affiliated with the program. There is coordination with school system personnel to assure the continuity of the program. Reporting on a one year experience with fifty girls affiliated with the program, Dr. Sarrel finds forty-two of the fifty girls returned to school with four having graduated. Five girls enrolled in a vocational training program. The most promising finding is that there was only one repeat pregnancy.

This model clinic is being expanded and refined to include a research component. Approximately twelve other hospitals are experimenting with new and more effective means of providing health service to the young unwed mother who seeks out clinic assistance.

The American Medical Association Council on Medical Service in its report to the House of Delegates, suggested a comprehensive attack on what it has termed "the national problem of pregnancy." Recommendations included research in underlying causes, prevention and understanding of the factors leading to illegitimacy, development of adequate facilities for caring for unmarried mothers, counselling service for the unmarried father, and distribution of a definitive approach to physicians for providing health care to unwed parents.

The American Medical Association recommendations pinpoint the problem pertaining to the great number of middle and upper income young unweds who do not go to clinics providing comprehensive medical and counselling services. It behooves the obstetrician to become more knowledgeable of the variety of counselling and rehabilitation services offered by the maternity home and adoption agencies listed in this article. Literature is available to the physician from these agencies which would be helpful for the physician as well as the unwed mother and her family. Regardless of economic status the family needs guidance when the unwanted pregnancy occurs.

If the unwed mother can be helped through medical care along with rehabilitation and counselling everyone stands to gain. Parents, in particular, should be made aware of the resources available to them so that plans can be evolved to prevent a repeat experience, and to offer the individual assistance necessary to help the patient and family realize their potential in a healthful manner.

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Licensed Child-Placing Agencies in Connecticut

FAIRFIELD COUNTY

State Welfare Department
434 State St., Bridgeport

Catholic Charities
(Bridgeport Diocese)
250 Waldemere Ave., Bridgeport
92 Main St., Danbury
606 West Ave., Norwalk
78 Elm St., Stamford

Children's Services of Connecticut
75 West St., Danbury
3 Ann St., South Norwalk

Family and Children's Services of Stamford
79 Worth St., Stamford

Greenwich Center for Child and Family Service
40 Arch St., Greenwich

Jewish Social Service of Bridgeport
1188 Main St., Bridgeport

Woodfield Children's Village
1899 Stratfield Rd., Bridgeport

HARTFORD COUNTY

State Welfare Department
60 Arch St., Hartford

Diocesan Bureau of Social Service
(Archdiocese of Hartford)
244 Main St., Hartford
259 Main St., New Britain

Children's Services of Connecticut
1680 Albany Ave., Hartford

Family Service of New Britain
33 Court St., New Britain

Jewish Social Service of Hartford
91 Vine St., Hartford

LITCHFIELD COUNTY

State Welfare Department
352 Main St., Torrington

Diocesan Bureau of Social Service
(Archdiocese of Hartford)
225 Main St., Torrington

Children's Services of Connecticut
105 Church St., Torrington

MIDDLESEX COUNTY

State Welfare Department
Main St. Ext., Middletown

Diocesan Bureau of Social Service
(Norwich Diocese)
50 Washington St., Middletown

NEW HAVEN COUNTY

State Welfare Department
194 Bassett St., New Haven

Diocesan Bureau of Social Service
(Archdiocese of Hartford)
36 East Main St., Ansonia
69 East Main St., Meriden
478 Orange St., New Haven
56 Church St., Waterbury

Children's Center
1400 Whitney Ave., Hamden

Jewish Family Service of New Haven
152 Temple St., New Haven

Lutheran Social Service
305 St. Ronan St.,
New Haven

NEW LONDON COUNTY

State Welfare Department
279 Main St., Norwich

Diocesan Bureau of Social Service
(Norwich Diocese)
42 Jay St., New London
62 Broadway, Norwich

Children's Services of Connecticut
302 State St., New London

TOLLAND COUNTY

State Welfare Department
Refer to Norwich office:
279 Main St., Norwich

Children's Services of Connecticut
Refer to Hartford Office:
1680 Albany Ave., Hartford

Diocesan Bureau of Social Service
Refer to Norwich office:
62 Broadway, Norwich

WINDHAM COUNTY

State Welfare Department
Refer to Norwich office:
279 Main St., Norwich

Children's Services of Connecticut
Refer to Hartford office:
1680 Albany Ave., Hartford

Diocesan Bureau of Social Service
Refer to Norwich office:
62 Broadway, Norwich

In towns where there are no local offices of the agencies above, refer to those nearest in the county.

(Note: There are other agencies in Connecticut serving unmarried parents but those listed here are the only ones authorizd to place children for adoption.)

Medicine undertakes the prolongation of Man's life but this extended life should be active, functional and creative. —A. L. Miasnikov.

THE PRESIDENT'S PAGE

On June 23, 1967, in Berkeley, California, a bit of einsteinium was bombarded in the heavy-ion linear accelerator by helium nuclei. The meeting of these stable elements did not cause destruction but rather created something new and interesting and powerful: mendelevium, with an atomic weight of 258, the heaviest substance ever positively identified, and with a radio-active half-life of about two months. Involved here along with the strictly scientific accomplishment are the names of Albert Einstein, Gregor Mendel of Austria, and Dimitri Mendeleev of Russia. The acceptance of einsteinium of two more protons and two more neutrons has altered the nature of this heavy metal and increased its potential. With time—and no further disturbance—it will return almost to its former state—never quite! Meanwhile it may use this added potential. To continue this use it needs further periodic stimulation.

In Washington on September 8th was held the plenary session of an International Conference on Abortion sponsored by the Harvard Divinity School in co-operation with the Joseph P. Kennedy, Jr. Foundation. During the two preceding days seventy-five individuals from this and five foreign countries, from a variety of religious and ethnic backgrounds, from the fields of medicine, law, ethics and the social sciences had exchanged in small groups the results of their experience and thought. The summaries of these discussions presented in the morning and the vignettes of pertinent cases in the afternoon called forth two observations of interest.

Each of us through exposure to custom, education, discipline—call it environment—has developed rather set standards, practices and ideas. How much more established must these be in one who has devoted a lifetime to studying a special subject! Yet that Friday more than one eminent and learned participant confessed to having had his fixed concepts shaken, thrown into doubt, even reversed. Not all in the same direction either! To have a Jesuit priest, Father Drinan of the Boston College Law School, propose repealing the prohibition of abortion during the first six months of pregnancy was indeed a surprising and bold departure. The collision of these heavy mental masses—these brilliant minds—was accelerating the production of fresh active concepts which radiate love and compassion for mankind.

Then Carl Kaysen of the Institute for Advanced Study, in reporting for the colloquium of the social sciences, sounded the keynote to the abortion question. Any discussion of abortion, if it is to be useful, must encompass the broadest range of family and community circumstances. When does the fetus become a human being with rights? If it has a right to life, will it receive the proper TLC? Will its life be "human"? If a mother has a right to protect herself and her children from an invader, is she entitled to protection from a fetus whose birth might administer the final crushing blow to an already tenuous family life? Life must have dignity and reverence. What is being, or should be, done to correct the situations which lead to the desire for abortion?

Obstetrician Andre Hellegers of Georgetown University pointed out that medicine until recently has been oriented to disease and death. The shift now is toward health—the physical, mental and social well-being of the *whole* individual. The problems surrounding the abortion question need the most experienced people to continue discussion—their minds unleashed and hungry.

Let not a "meeting of the minds" be an acquiescence, but a joining of forces directed toward a higher goal. Abortion is only one of the problems of our people that needs thought and action. What others can *you* think of where the need is crying? Tell me or your Councilor so we can try to be constructive through a collision of the minds.

E. Tremain Bradley, M.D.

FROM THE GENERAL MANAGER'S OFFICE

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CALL

SEMI-ANNUAL MEETING OF THE HOUSE OF DELEGATES

The 1967 Semi-Annual Meeting of the House of Delegates will be held at the Holiday Inn, 404 Bridge Street, Groton, commencing at 2:00 o'clock in the afternoon of Wednesday, December 13.

E. Tremain Bradley, President
Kenneth F. Brandon, Speaker of the House
Charles Polivy, Secretary

INTRODUCTION OF RESOLUTIONS

Article V, Section 12, Par. 3 of the Bylaws of the Society Provides that:

All resolutions to be considered as regular business at any regular meeting of the House of Delegates must be in the hands of the Speaker not later than seventy-two hours before the opening of that meeting. All resolutions and recommendations published in the official agenda distributed to the members of the House prior to the meeting at which action is to be taken shall be considered as regular business. Resolutions presented later than seventy-two hours before the opening of a meeting will be referred for consideration as regular business by the House only when they are presented by the Council or accepted for consideration by majority vote of the delegates present. Any resolution which does not qualify in accordance with the aforesaid provisions for consideration as regular business may be accepted for action by a majority vote of the delegates present and, if so accepted, shall be referred at once by the Speaker to a reference committee. Any such reference committee shall consider resolutions referred to it and shall report, with recommendations to the House before adjournment of the meeting.

PROPOSED AMENDMENTS TO THE BYLAWS

The following proposed amendments to the Bylaws were presented to the House of Delegates on April 25, 1967 and were tabled for consideration and action at the next regular meeting of the House of Delegates.

In accordance with the Bylaws, these amendments will be published in Connecticut Medicine, "on one or more occasions prior to the next meeting . . . at which meeting the amendment shall be taken off the table and acted upon by the House of Delegates."

INTRODUCED BY THE COUNCIL

RE: ESTABLISHMENT OF A JUDICIAL COMMITTEE AND OUTLINING PROCEDURES PERTAINING TO SAME.

PROPOSED AMENDMENT

Article VII—The Council.

Section 1. Powers and Duties.

Par. 4. Censorship: The Judicial Committee shall be the Board of Censors of the Society. All questions of an ethical nature brought before the House of Delegates or a general meeting shall be referred to the Judicial Committee without discussion. It shall hear and decide all questions of discipline affecting the conduct of members of component associations on which an appeal is taken, and its decision in all such matters shall be final.

The Judicial Committee shall serve as a board of review from cases of claimed malpractice referred to it by the committee on medical ethics and deportment of any component county associations.

PRESENT BYLAW

Article VII—The Council.

Section 1. Powers and Duties

Par. 4—Censorship.

"The Council shall be the Board of Censors of the Society. It shall consider all questions involving the rights and standing of members in relation to other members, to the component associations, or to this Society. In addition, all questions of an ethical

nature brought before the House of Delegates or a general meeting, shall be referred to the Council without discussion. It shall hear and decide all questions of discipline affecting the conduct of members of component associations on which an appeal is taken, but only on questions of law and procedure and not on facts and its decision on all such matters will be final.

(a) The Council shall consider only the records of the component medical association in the proceedings involved.

(b) It shall determine that the record available to them is material and sufficient to support the findings which the component medical association reached.

(c) If determining that the above procedure was correct, it shall make its findings known to the appellant.

(d) If, however, finding that the procedure was not material or sufficient, it shall remand the case to the component medical association and ask for a new hearing.

(e) No appeal shall be considered or reviewed until such time as the component medical association has made its decision as to the facts in the case.

The Council shall also serve as a board of review for cases of claimed malpractice referred to it by the committee on medical ethics and deportment of any component county association."

PROPOSED AMENDMENTS

Article X—Committees of the Council.

Section 1. No change.

Section 2. Standing Committees of the Council.

Par. 1. Outline

Change "A Committee on Preliminary Study of Censorship Questions" to read "A Judicial Committee"

Par. 2. Membership. The members of all standing committees of the Council shall be discharged automatically upon the adjournment of the annual meeting of the House of Delegates following their election except for the Judicial Committee.

Par. 7. Committee on Preliminary Study of Censorship Questions (delete and insert the following:)

Par. 7. Judicial Committee

a. Composition. The Judicial Committee shall consist of twelve members of the Society. Each must have been a member of the Society for 10 years and have served as an officer of the Society or of a component association. Initially, the Council shall elect one member from each component association and four members-at-large each to serve until his seat is filled by Council election in one, two, three, or four years. Annually, thereafter, the Council shall elect one member from each of two component associations in quadrennial rotation, and one member-at-large, each to serve a four year term. No member shall serve more than two consecutive terms. The Council shall appoint the Chairman for a term of two years but shall not reappoint the same Chairman more than twice in succession.

b. Jurisdiction: The judicial power of CSMS shall be vested in the Judicial Committee, with jurisdiction over all members of the CSMS, acting within its functions. Its decision shall be final and binding, except that members of the AMA shall have those rights of AMA members. In case of appeal to the AMA, any decision shall be stayed until such procedures have been exhausted according to the AMA Constitution.

c. (1) Functions: To interpret all questions of medical ethics. The Judicial Committee may study and render an opinion when indicated on any question referred to it from the Council or from any other responsible source on its own motion involving the rights, standing, or obligations of members in relation to other members or to the component association or to the Society or any subdivision thereof, or on any question of an ethical nature or affecting the good name of the profession, or on any appeal of a question of discipline affecting the conduct of a member of a component association, or on any litigation arising out of a physician's practice. Its opinions shall be binding on the parties concerned and specific problem considered, but shall be considered only as a presumption of the Society, binding on all members only when endorsed by the Council and published in "Connecticut Medicine". The Judicial Committee may use its judgment whether or not to request such endorsement from the Council.

(2) To interpret the Constitution (Charter), Bylaws and Rules of CSMS and the component county associations: to decide any dispute or questions between the CSMS and county association, or between county associations.

(3) Investigating Jury: The Judicial Committee, acting on its own motion or on request from any responsible source, may request the President to appoint a jury to investigate and report on any complaint or condition in the state of greater than local concern affecting the profession as a whole. If the jury finds that there is probable cause for action, it shall so state. The President shall in turn submit the report to the Judicial Committee. If it agrees that there is need for action, it shall first request the county medical society having

jurisdiction to take appropriate action and to submit a report of the facts found and the action taken. The Judicial Committee may act in its appellate function as to any action taken by the county in the matter.

(4) The Judicial Committee shall represent the Society on the Physician-Hospital Mediation panel. The chairman may appoint an ad hoc subcommittee of three members, who shall be impartial as to subject matter, persons involved and other prejudicial factors, to assist in resolving disagreements involving members of the Society when those procedures recommended by the Joint Commission on Accreditation of Hospitals have failed.

(5) The Judicial Committee shall render an annual report to the Council including its actions, opinions, and recommendations and shall make such interim reports as it desires or as are requested by the Council. Such reports shall be available to members of CSMS.

d. Procedure: A majority shall constitute a quorum. The Committee shall meet at least bimonthly. The President shall fill any vacancy. The Committee, in any ethical problem, which in its judgment transcends medical ethics, may invite discussants and participants, lay as well as medical.

PRESENT BYLAW

Par. 7. Committee on Preliminary Study of Censorship Questions. *When the Council receives a question involving the rights and standings of members, in relation to other members or to the component associations or to The Society, or when a question of an ethical nature is referred to the Council from the House of Delegates, or when an appeal is taken to the Council on a question of discipline affecting the conduct of members of component associations, or when a case of claimed malpractice is referred to the Council by the committee on medical ethics and deportment of a component association, the Council shall elect a Committee on Preliminary Study of Censorship Questions which shall study and review such question or appeal or claimed malpractice case and shall report its findings and recommendations to the Council. Once such committee is elected, it shall serve as a standing committee of the Council.*

PROPOSED AMENDMENT

Article XIV—Component Association

Section 7. Discipline

Par. 1. Appeal

Any member of the Society aggrieved by disciplinary action of the component association of which he is a member shall have the right of appeal to the Judicial Committee of the Society, which shall review the proceedings and render a decision concerning the disciplinary action taken; this shall be final, in its jurisdiction, except that members of the American Medical Association may appeal to the Judicial Council of the AMA.

Par. 2. Procedure

Procedure: An appeal shall be in writing, signed by the appellant. The appellant must send (within ten (10) days of notice of the decision) a copy of his intent to appeal to the Secretary of his Association, and to the General Manager of the Society who shall immediately notify the Chairman of the Judicial Committee. The County Association shall then prepare a concise summary of the case, giving the charges, the relevant facts found in the hearing, and the principle of ethics of which the accused was found guilty of violating. It shall send a copy to the appellant and to the Judicial Committee within thirty (30) days of the appellant's letter of intent to appeal. The appellant shall send a copy of his brief to the General Manager for the Judicial Committee, and to the Secretary of his Association; specifying the procedures, findings of fact, conclusions or disciplinary action or any part thereof that is questioned or challenged within thirty (30) days of the date the County Association has sent a copy of its summary to him. All unchallenged evidence or matter material to the charges in the proceedings shall be presumed to be accepted and admitted as factual. On request by the Judicial Committee the Association shall furnish all records (or copies) of the proceedings and other pertinent material. Such records shall be made available to the defendant. The Committee may remand either brief to the appropriate party with instructions.

The filing of an appeal shall automatically stay the execution of the original decision until all the appeals including one to the AMA, shall have been acted upon. Appeals to the AMA must be made in accordance with their rules.

The Judicial Committee may restrict itself to the issues raised in the briefs and make its decision thereon. But if either party requests to appear in person, both parties shall be invited to appear before the Judicial Committee after proper notice, not less than ten (10) nor more than thirty (30) days. Each party shall be entitled, upon application and for cause shown, to reasonable adjournment of such a hearing.

The Judicial Committee may limit the proceedings to the oral argument, relevant and supplementary to their briefs, allotting thirty (30) minutes for each party, or may extend the hearing on request or on its own initiative, by majority vote, as long as necessary to insure that its verdict is just and fair.

It shall not be the purpose of the Judicial Committee to re-try the case but rather to determine that the hearing by the county was fair. It shall have appellate jurisdiction in questions of law and procedure, only setting aside questions of fact when, in its opinion, such findings are not supported by a preponderance of evidence. Under exceptional circumstances and at its own discretion, the Committee may call up witnesses and elicit such testimony as may be considered necessary to arrive at a fair and considered judgment. It may remand the case to the Association with instructions whenever or for any part of the proceedings it decides necessary.

The Committee is authorized to use legal counsel. The defendant may be represented by a member of the Society and/or be accompanied by legal counsel who may advise but not participate in the proceedings. The defendant may enter objections in the course of the proceedings. The appellant may be assisted in preparing his brief and appeal. The Committee shall not be bound by legal rules of evidence.

The members of the Judicial Committee shall be impartial to the parties and to the substance of the charges. If anyone shall disqualify himself or be disqualified for cause on challenge, the President of the Society shall appoint a substitute.

If either party shall refuse to cooperate or fail to appear without cause, acceptable to the Committee, the Committee may proceed, dismiss, or decide the case. The Committee may request any member of the Society to appear and answer reasonable questions; refusal or failure without cause acceptable to the Committee to cooperate shall be considered unprofessional conduct.

The Judicial Committee shall decide by written ballot. Only those present throughout the hearing shall vote; a majority shall be necessary to overrule the County. It shall vote first on the decision as to guilt; then as to the penalty. It may affirm or reverse the verdict, and modify the penalty or make such other disposition as it deems proper. It shall notify the parties of its decision by registered mail within ten (10) days of completion of the hearing.

Any member of the Society, in any proceeding before any committee or association of the Society or component thereof, which is disciplinary in character or might reflect in any manner on his honor or reputation as a physician or person, shall be entitled to the following principles of fairness and procedure, reasonably detailed in practice: notice, written charges, a hearing before an impartial tribunal, the right to be present throughout the hearing, to reasonably cross-examine witnesses, to present witnesses and other reasonable means to defend himself, the right to be represented by a medical colleague and to be advised by legal counsel. The Judicial Committee of the Society shall require, in any appeal, that the previous proceedings have been conducted in a manner consistent with the principles of justice herein above expressed.

All dates shall be considered post-dates.

The Judicial Committee shall complete an appeal and notify the parties within four (4) months of the appellant's letter of intent to appeal.

PRESENT BYLAW

Section 7. Discipline

Any member of a component association who is aggrieved by disciplinary action of the component association of which he is a member shall have the privilege of appealing to the Council of the Society which shall review the charges made against the disciplined member and the findings therein and render a decision concerning the disciplinary action taken; this shall be final.

1967 Meetings

October 25—Semi-Annual meeting of the New Haven County Medical Association to be held at the Waverly Inn, Cheshire, Connecticut. Business meeting beginning at 3:30 P.M. **Please Note:** Date of meeting has been changed from October 26 to October 25.

1968 Meetings

April 30, May 1-2—176th Annual Meeting of the Connecticut Medical Society to be held at the Hartford-Hilton Hotel, Hartford, Connecticut.

PLACEMENT WANTED

SURGEON — Board certified in General and Thoracic Surgery wishes a group or associate type practice in a coastal town. Interested in peripheral vascular, cardiac and thoracic surgery. Has applied for Connecticut license. Military obligations completed.

G.P. — 49 years of age, applied for Connecticut license. Would like to practice in a large or medium-sized community in an associate or group practice situation.

INTERNIST — 43 years of age, Board eligible. Wishes to practice with a group or an individual. Excellent training in Cardiology. Connecticut license.

PLACEMENT OPPORTUNITIES

INTERNIST — Board certified or eligible, military obligations completed. Three year partnership offered to right man in a Southern Connecticut town.

WANTED — young internist, Board eligible or certified to associate with two other young internists in modern, fully equipped building in suburb of Hartford.

FULL TIME Health Director needed for brand new regional health district in picturesque Connecticut. Handy to fine schools, colleges, Berkshire Mountains, salt water, skiing, golfing, music centers, etc. Salary $18,500 per annum. Apply to: Fowler F. White, M.D., Acting Director; Torrington Regional Health District; 59 Field Street; Torrington, Connecticut 06790 or phone 203-482-4441.

PSYCHIATRIST — challenging position open at modern Connecticut penal institution. Opportunity to organize and develop treatment program. Salary range up to $20,500. Outstanding retirement and fringe benefits. Must have three years' residency training in a center acceptable by American Board of Psychiatry and Neurology and a year as staff psychiatrist; eligible for Connecticut license. Write: S. Stein, State Personnel Department, 405 State Office Building, Hartford, Connecticut 06115.

INTERNIST — to act as consultant to medical profession, hospital and nursing home administrators to assure creation and effective functioning of hospital services for participation in the Hospital Insurance Program; assists with formation of utilization review committees and reviews proposed plans of hospitals and extended care facilities; surveys institutions participating in the Health Insurance for the Aged Program and provides professional guidance to a medical staff, administrators, and owners concerning medical records, policies, and utilization review plans; evaluates medical staff organization; participates in educational programs for professional and sub-professional staff of health care facilities; prepares and studies reports. Excellent salary good fringe benefits and retirement program. Contact: State Personnel Department, State Office Building, Hartford, Connecticut 06115 for further information.

MEDICAL DIRECTOR — Full time Medical Director for the Child Guidance Clinic for Central Connecticut, Inc. Board certification not required. Experience with child psychiatry preferred. Regular hours, qualified staff. Progressive mental health community. Salary $18,000-$25,000, with excellent fringe benefits. Contact Mrs. B. H. Hunt, Personnel Chairman, Child Guidance Clinic for Central Connecticut, Inc., 116 Lincoln Street, Meriden, Connecticut 06450.

MEDICAL DIRECTOR of manufacturing corporation in New Britain area. Internal Medicine training preferred but not necessary. Duties clinical, with nursing staff, sick room and lab facilities. $20,000 plus stock options, retirement, etc.

ASSISTANT MEDICAL DIRECTOR of insurance company division, Hartford, Internal Medicine training preferred, but not necessary. Duties clinical. $18,000 plus fringe benefits.

ASSISTANT SURGICAL DIRECTOR of insurance company division. $22,500 plus fringe benefits. Some administrative experience. Duties clinical and administrative.

HOUSE PHYSICIAN — Diversified duties in accredited, voluntary hospital. Connecticut license required. Monday through Friday, every other Saturday morning. $18,000 a year. Write: P.O. Box 3474, Bridgeport, Connecticut 06604.

PATHOLOGIST — full time or part time, to direct a clinical laboratory in an 1800-bed mental hospital. Ample opportunity for research and teaching available. Well equipped and staffed laboratory. Emphasis on Neuropathology. Board certified or eligible pathologist preferred. Starting salary range: $16,460-$19,760. Excellent fringe benefits. All particulars in first letter, including references. Contact: Mehadin K. Arafeh, M.D., Superintendent, Connecticut Valley Hospital, Box 351, Middletown, Connecticut 06458.

RADIOLOGIST — 450-bed general hospital needs a fourth radiologist to do general diagnostic radiology in new nine room Department which is now under construction. The Department does approximately 125 examinations a day, including special procedures. A younger, Board qualified or certified man is needed now to achieve parity with other radiologists at end of three years. Practice is full time in the hospital. Contact: Howard F. Root, Jr., M.D.; c/o Department of Radiology; New Britain General Hospital; New Britain, Connecticut 06052. Telephone 223-2761.

PATHOLOGIST — State of Connecticut centrally located general hospital. Must have two years' employment in pathology; be eligible for Connecticut license. Salary range: $16,460-$22,180 plus many extras. Write S. Stein, State Personnel Department, 405 State Office Building, Hartford, Connecticut 06115.

ANESTHESIOLOGIST — Board eligible or certified to join small partnership in private practice at the Windham Community Memorial Hospital, 112 Mansfield Avenue, Willimantic, Connecticut 06226. A progressive growing hospital in a community with a State College and the University of

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Connecticut only 8 miles away. For further information, contact William Grillo, M.D. or Samuel Dodd, M.D. at the Windham Community Memorial Hospital, Willimantic, Connecticut — Telephone 423-9201.

PEDIATRICIAN urgently needed for community 15 minutes from Hartford with population area of 45,000 people. Opportunity available to head Pediatrics Department in hospital undergoing extensive construction program. Congenial medical staff will help establish. Write: Secretary, Medical Staff, Rockville General Hospital, Rockville, Connecticut 06066.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

Doctor's Office

Jachin B. Davis, M.D., announces the removal of his office for the practice of obstetrics and gynecology to University Towers, 100 York Street, New Haven.

Robert William Harkins, M.D., announces the opening of an office for the practice of internal and family medicine at Judson Avenue, Woodbury.

Ronald J. Pimpinella, M.D., announces the opening of an office for the practice of otorhinolaryngology or surgery for diseases of the ear, nose and throat at 106 Litchfield Street, Torrington.

Martin W. Sklaire, M.D., announces the opening of an office for the practice of pediatrics at the Madison Professional Building, Wall Street, Madison.

David M. Silverstein, M.D., announces the opening of an office for the practice of neurological surgery at 5 Maple Avenue, Derby.

Joseph B. Whibey, M.D., announces the removal of his office for the practice of surgery to the Waterbury Medical Building, 1389 West Main Street, Waterbury.

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Ethics For Doctors' Wives

All activities of any Auxiliary must be bound by the Principles of Medical Ethics.

Just as physicians individually and collectively must maintain a high level of ethical conduct in their relationship with patients, colleagues, members of allied professions and the public, so must the wives of physicians, individually and collectively, maintain this code of conduct.

Discretion and good judgement should automatically dictate the proper attitude and course of action for an Auxiliary or an individual member concerning problems of medical ethics.

The doctor's wife must fully understand that her husband, as a physician, is obligated to hold in trust the confidences concerning his patients and that the principal objective of the medical profession is to render service to humanity with full respect for the dignity of man.

Under the guidance of the medical profession the auxiliary and individual members are obligated to make available to the public information on better health care.

The physician's wife should endeavor at all times to uphold the dignity and honor of the medical profession and accept its self-imposed discipline even in casual and social situations.

The wife of a physician should never solicit patients nor criticize the treatment or conduct of another physician in regard to his patients.

The honored ideals of the medical profession imply that the responsibilities of the physician extend not only to the individual, but also to society. His interest and participation in activities which have the purpose of improving both the health and the well being of the individual and the community are essential and are his responsibility. The physician's wife functions as a partner in fulfilling this obligation.

The Woman's Auxiliary and the individual member is the public representative of the medical profession. The attitude of the public toward the medical profession is greatly dependent on the attitude and behavior of the physician's wife and family.

Assisting the patient to locate a physician in an emergency is an obligation of the physician's wife in the absence of her husband.

Constant telephone calls are often a source of irritation but should be handled with tact and patience.

Inquiries regarding a patient's state of health by friends or families should be tactfully referred to the physician.

Good taste and moderation, both at home and in public, should be observed by the physician's family.

Treatment and diagnosis should be left to the discretion of the physician and should never be indulged in by a member of his family.

Active community participation and leadership is essential to good citizenship and should be a primary concern of the auxiliary member.

The community programs and projects of the medical society and auxiliary should have the unqualified support of every physician's wife.

By furthering friendly relations among doctors' families you will help your husband carry out the principle in the Hippocratic Oath which reads, "My colleagues will be my brothers."

Extend hospitality to the wives of medical students and young physicians.

Provided you are not professionally employed in your husband's office, frequent visits can be regarded as snooping by patients and employees.

Patient information is privileged information and should go no further than the file.

Tactful guidance of office personnel is rarely possible. Leave such matters to the physician and the medical assistants society.

Hospital regulations and privileges are made for the benefit of the patient and should be courteously observed—especially by physicians' wives.

Have a friendly attitude toward nurses and medical assistants.

when bursitis hits a 280-lb. tackle,

hit back with Butazolidin alka

Indications: Osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, psoriatic arthritis, acute gout, painful shoulder (peritendinitis, capsulitis, bursitis and acute arthritis of that joint), acute superficial thrombophlebitis.

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently. Large doses of Butazolidin alka are contraindicated in glaucoma.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Before prescribing, carefully select patients, avoidin
those responsive to routine measures as well as contraindicated p
tients. Obtain a detailed history and a complete physical and laborato
examination, including a blood count. The patient should not excee
recommended dosage, should be closely supervised and should b
warned to discontinue the drug and report immediately if fever, so
throat, or mouth lesions (symptoms of blood dyscrasia); sudden weig
gain (water retention); skin reactions; black or tarry stools or oth
evidence of intestinal hemorrhage occur. Make regular blood count
Discontinue the drug immediately and institute countermeasures if th
white count changes significantly, granulocytes decrease, or immatu
forms appear. Use greater care in the elderly and in hypertensive

Adverse Reactions: The most common are nausea, edema and dru
rash. Swelling of the ankles or face may be minimized by withholdin
dietary salt, reduction in dosage or use of diuretics. In elderly patien
and in those with hypertension the drug should be discontinued wit
the appearance of edema. The drug has been associated with peptic u

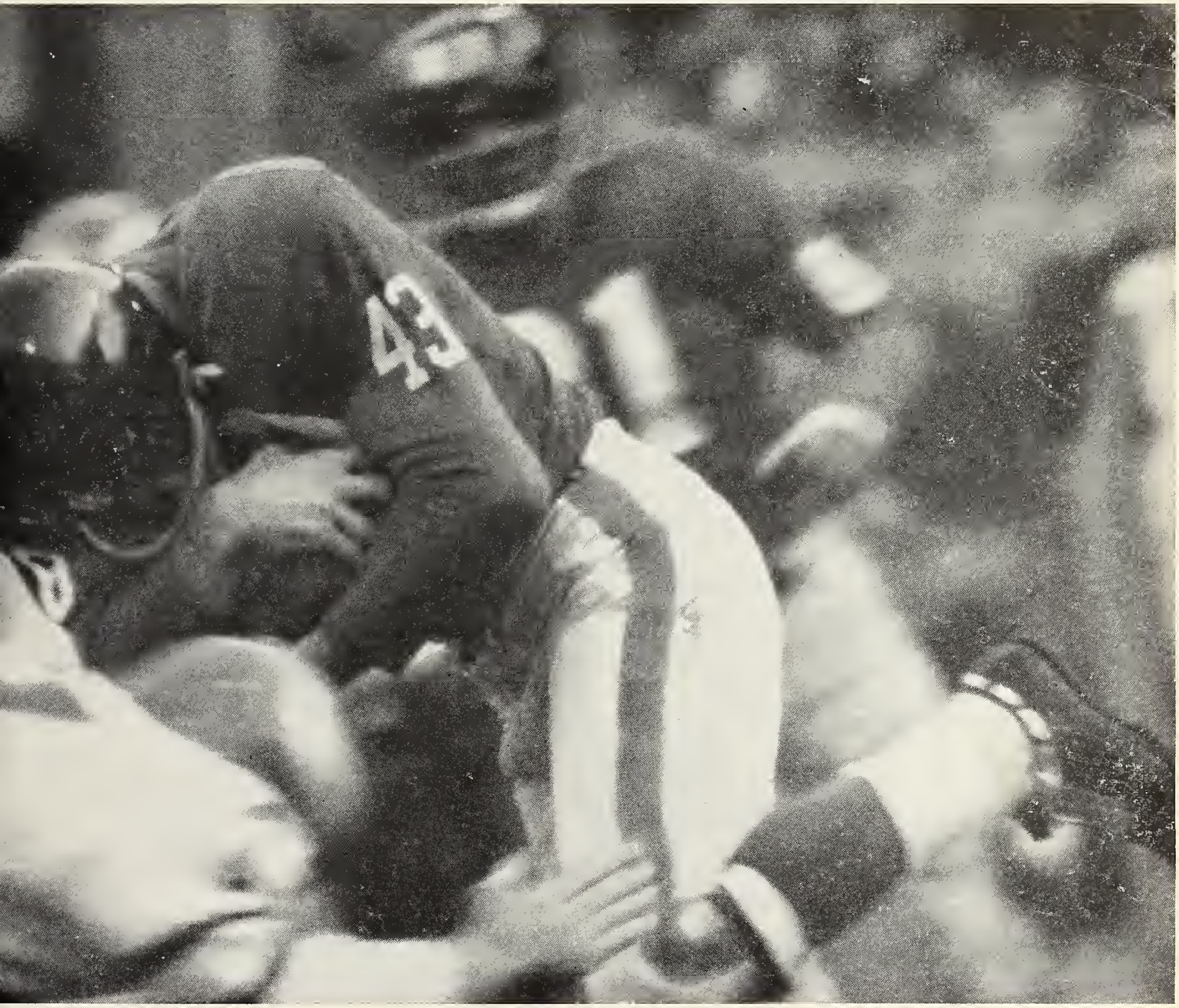
**r 280-lb. tackles—or 108-lb. housewives—Butazolidin alka can hasten recovery from the
ionizing pain of shoulder bursitis.**

**s not for every patient. Check carefully the Contraindications, Warning and
ecautions shown below.**

**d adverse reactions may occur. The most common are nausea, edema and rash.
rely, agranulocytosis has been reported. All adverse reactions are listed below, too.**

**ay-for-pay or workaday patients—when they come up with shoulder bursitis and your
nical judgment indicates Butazolidin alka—go with it.**

d watch the comeback.



ınd may reactivate a latent peptic ulcer. The patient should be in-
ted to take doses immediately before or after meals or with
to minimize gastric upset. Mild drug rashes frequently subside
reduction of dosage. However, rash accompanied by fever or
r systemic reactions usually requires withholding medication.
uric rash has also been reported. Agranulocytosis, exfoliative
ıatitis, Stevens-Johnson syndrome, or a generalized allergic re-
on similar to serum sickness may occur and require permanent
drawal of medication. Stomatitis, salivary gland enlargement,
ting, vertigo and languor may occur. Leukemia and leukemoid
tions have been reported. While not definitely attributable to the
, a causal relationship cannot be excluded. Thrombocytopenic
ura and aplastic anemia may occur. Confusional states, agitation,
lache, blurred vision, optic neuritis and transient hearing loss have
.reported, as have hyperglycemia, hepatitis, jaundice, and several
s of anuria and hematuria. With long-term use, reversible thyroid
rplasia may occur infrequently. Moderate lowering of the red cell
t due to hemodilution may occur. 6509-V(B)R2

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100 mg.	phenylbutazone
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Dosage in painful shoulder: Initial: 3 to 6 capsules daily in 3 or 4 equal doses. Trial period: 1 week. Maintenance dosage should not exceed 4 capsules daily; response is often achieved with 1 or 2 capsules daily.

For complete details, please see full prescribing information.

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We can assume our husbands are intelligent. They had to be, to meet the requirements of their profession. They are not greedy. If they were, they would have not chosen medicine as a profession, for they could make more money on a smaller investment of capital and effort. Our husbands like their work and all the obligations it entails. They are willing to take time and trouble with individuals.

We wives have a part in this profession in helping our husbands live up to their code of ethics—the only set of morals that has remained unchanged since its inception. We have an obligation to the sick, to the pioneers of medicine, to the teachers who have collected the knowledge of the ages and delivered it ready-made to our husbands, and to the thousands of other physicians throughout the world who are trying to bring honor to the name of doctor. We can help to promote the spirit of Luke rather than Midas.

It does not follow that we are a privileged class, but on the contrary, the community can expect more of us because we are a member of a doctor's family.

The interpretation of ethics for doctors' wives is personal in complexion, yet its underlying principles are evident to all of us.

(*reprinted from*):

Woman's Auxiliary AMA Member Orientation Manual.

Special Notices

DIABETES WEEK

November 12-18, 1967

Diabetes Week will be observed nationally November 12-18. Dr. Edwin W. Gates, Niagara Falls, New York, President of the American Diabetes Association, will address a joint meeting of the Connecticut Diabetes Association and the New Haven Medical Association Wednesday evening, November 1, inaugurating Diabetes Week in Connecticut.

CONNECTICUT CHAPTER OF THE NATIONAL HEMOPHILIA FOUNDATION

October 18, 1967

Morning Session—10:00 A.M. to 1:00 P.M.

Concepts of Coagulation and the Laboratory Diagnosis of Coagulation Defects
Management of Bleeding in Hemophilia
New AHG Concentrates and Their Use

Afternoon Session—2:00 to 4:30 P.M.

Management of Orthopedic Problems in Hemophilia
Psychiatric Problems in Hemophilia
Management of Dental Problems in Hemophilia
Hemophilia Genetics and Genetic Counseling

To be held in the Mary S. Harkness Memorial Auditorium at Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut. All interested physicians are invited to attend. Advance registration is not required, and no fees will be charged. Physicians on call may be reached at telephone number 562-1151, extension 440.

Sponsored by the Connecticut Chapter of the National Hemophilia Foundation and Yale University School of Medicine.

SYMPOSIUM ON PEDIATRIC ALLERGY

St. Francis Hospital — Department of Pediatrics

114 Woodland Street, Hartford, Conn.

Wednesday, November 15, 1967

9:30 Registration

9:45 Introduction
William J. Lahey, M.D., Director of Medical Education
Joseph C. Cullina, M.D., Chairman, Department of Pediatrics

10:00 "Atopy and the General Nature of the Allergic State"
Raymond D. A. Peterson, M.D.,
Director of Research
LaRabida—University of Chicago Institutes
Chicago, Illinois

11:00 Coffee

11:30 "Excema and Other Allergic Dermatologic States."
Harold I. Lecks, M.D.
Children's Hospital
Philadelphia, Pennsylvania

12:30 Luncheon

1:30 "Asthma and Related Respiratory Conditions"
Leonard S. Girsh, M.D.
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

2:30 Intermission

3:00 Panel Discussion

Moderator: William E. Hart, M.D., Chairman of Education, Department of Pediatrics

Panelists: Leonard S. Girsh, M.D.
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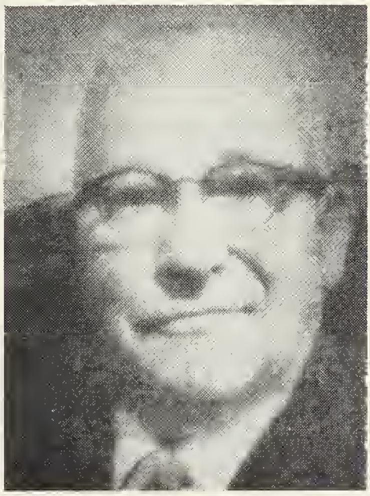
OBITUARIES

Harold B. Woodward, M.D.

1887-1967

Dr. Harold B. Woodward, age 80, of Pinehurst Road, Bristol died in Bristol Hospital August 1, 1967 from congestive heart failure.



He was born in Terryville, Connecticut, February 13, 1887. He graduated from Bristol High School in 1904, received his B.S. in 1908 from Wesleyan University, and M.D. in 1912 from John Hopkins Medical School. He interned in Waterbury Hospital and the following year opened his office in Terryville for the general practise of medicine. Dr. Woodward was appointed to the medical staff of Bristol Hospital in 1922.

He volunteered in World War I for the U.S. Army Medical Corps and sailed with the first contingent of troops to go overseas in Sept. 1917. He served in hospitals in England and with the British Army in France, holding rank of Captain on his discharge.

He then attended University of Pennsylvania for specialization in Diseases of Eye, Ear, Nose and Throat, and was named Attending Surgeon in this field in Bristol Hospital in 1929. He was also Attending Surgeon in New Haven Hospital and instructor in Ophthalmology and Clinical Assistant at Yale Medical School. During the period he practised his specialty in Bristol and retired in 1957.

In 1914 he married Nellie H. Birtch, R.N. of New Brunswick, Canada, who died in 1959. In 1960 he married Mrs. Lila Hubbard of Bristol, who survives him.

He was an ardent golfer and fisherman, and held membership in Pequabuck, Chippanee and Winter Park Golf Clubs. He was a member of Bristol Rotary Club and University Club of Winter Park, Florida, where he spent his winters following retirement.

He was a member of Bristol, Litchfield County, the Connecticut State Medical Society, and American Medical Association.

Dr. Woodward was highly regarded by his colleagues and his personal interest in his patients was deeply appreciated. He was a generous and kind man who advised and helped many families in Bristol and Terryville. His memory is cherished by his many friends.

WINFIELD E. WIGHT, M.D.

Warren A. Tanner, M.D.

1886-1967

Warren A. Tanner was born in Brooklyn, Connecticut on June 5, 1886, the son of Alfred and Lucy Tanner. His father, Alfred, was a practicing physician in Brooklyn, Connecticut. Dr. Warren attend the public school in Brooklyn, Connecticut and Killingly High School in Danielson, Connecticut from where he graduated in 1906. He then attended the University of Vermont and was graduated from the University of Vermont Medical School in 1912. His internship was at the Fanny Allen Hospital in Winooski, Vermont. He was then in general practice in Stamford, Connecticut in 1913 where he practiced for about one year. His father Alfred Tanner, M.D. then died, and he took over his father's practice in Brooklyn, Connecticut. He was married and his first wife and he lived together for less than one year following which they divorced. There were no children from this marriage.

In 1919 he was married to Bertha Boehme of Brooklyn, New York. He had one son Warren Avery, Jr. born July 13, 1920. Dr. Tanner spent fifty-four years in general practice in Connecticut; fifty-three of these in the towns of Danielson and Brooklyn. This he did in his own quiet, humble way and was admired by all. About ten years ago, he received the Man of the Year Award for service to the community by the Danielson Chamber of Commerce. Dr. Tanner continued to practice in Danielson until about six months ago, when he became too ill.

He was health officer for the towns of Killingly and Brooklyn for many years. He was a member of

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the Windham County Medical Association, the Connecticut State Medical Society and the AMA. His hobbies were collecting stamps and fishing. He died at the Day Kimball Hospital on June 23, 1967 of "arteriosclerotic heart disease and emphysema."

G. M. Chartier, M.D.

In Memoriam

Daly, Charles W.—Hartford; College of Physicians and Surgeons, 1910. He was a member of the consulting staff at St. Francis Hospital, and former president of the Hartford Board of Health. He was a member of the Hartford County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Daly died August 31, at the age of 74.

Gillson, Reginald E.—Branford; University of Vermont Medical School, 1929. Dr. Gillson was a prominent dermatologist and allergist in the New Haven area for 23 years. After retirement in June of 1965, he became associated with the Medical Department of Pratt and Whitney plant in North Haven. Dr. Gillson was a member of the staffs of the St. Raphael's and Yale-New Haven Hospitals. He was a member of the New Haven County Medical Association, the Connecticut State Medical Society, the American Medical Association, the American Academy of Dermatology, and fellow emeritus of the American College of Allergists. Dr. Gillson died September 12, at the age of 80.

Italia, Sebastian R.—Wethersfield, Yale University School of Medicine, 1957. Dr. Italia was a practicing surgeon and general practitioner in Hartford. He was vice president and on the Board of Directors of the Hartford Chapter of UNICO. He was a member of the Hartford County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Italia died September 11, at the age of 36.

Maiorano, Joseph F.—New Haven; New York Medical College, 1943. Dr. Maiorano was an orthopedic specialist in the New Haven area for many years. During World War II, he was a captain in the Medical Corps, serving in the European Theater. He was attending orthopedic physician at St. Raphael's Hospital and formerly was the physician for the East Haven High School football team. He was a member of the New Haven County Medical Association, the Connecticut State Medical Society, the American Medical Association, and a diplomate in Orthopedics. Dr. Maiorano died September 5, at the age of 49.

Mastrony, Paul C.—Bridgeport; Catholic University of Louvain Medical School, 1959. Dr. Mastrony was a psychiatrist and director of the Department of Physical Medicine at St. Joseph's Hospital, Stamford. He was a U.S. Army Veteran of World War II. He was a member of the Stamford Medical Society, the Fairfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Mastrony died August 26, at the age of 40.

BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Thiamine Deficiency: Biochemical Lesions and their Clinical Significance. Ciba Foundation, Study Group No. 28. Edited by G.E.W. Wolstenholme, O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1967. 163 pp. with 46 illustrations.

Endocrinology of the Testis. Edited by G.E.W. Wolstenholme, Ciba Foundation Colloquia On Endocrinology, Volume XVI. O.B.E., M.A., F.R.C.P., F.I. Biol. and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1967. 331 pp. with 93 illustrations. $12.50.

Development of the Lung. Ciba Foundation Symposium. Edited by A. V. S. de Reuck, M.Sc., D.I.C., A.R.C.S. and Ruth Porter, M.R.C.P. Little, Brown and Company, Boston, 1967. 408 pp. with 134 illustrations. $13.00.

Caste and Race: Comparative Approaches. A Ciba Foundation Volume. Edited by Anthony de Reuck and Julie Knight. Little, Brown and Company, Boston, 1967. 348 pp. illustrated. $12.00.

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NEW BOOKS IN REVIEW

SYNOPSIS OF PEDIATRICS. 2nd Edition. Edited by James G. Hughes, B.A., M.D. The C. V. Mosby Company, Saint Louis, 1967. 1099 pp. with 86 illustrations. $10.85.

Reviewed by: LOUIS H. NAHUM

The pace of modern medicine is rapid and it is difficult for even the most devoted physician to keep abreast of progress. The busy physician must read as he runs about. Books are legion but time is limited. Presentations that condense and crystallize important medical information are not always available. In this synopsis it is. It does not rival excellent pediatric reference texts which are indispensable to the specialist. And so this reference does not cover everything.

However, there is a strong orientation towards explanations of the fundamental mechanisms of disease which successfully bridges the gap between basic science and clinical pediatrics. This helps one to appreciate disease and explains the logic of correct therapy. Medical art has here given way to basic science.

This book, like the child, has grown in size because comprehensiveness is antithetical to brevity but it does contribute to clarity. There is an interesting method of medical illustration evolved by the Editor which consists of organ arrow and label overlays superimposed upon the picture of a child. It is an excellent method for making illustrations and teaching slides.

When one compares the first edition of four years ago with this, one finds extensive revisions and new material and many sections have been rewritten. New chapters have appeared on autosomal abnormalities, cancer in childhood and the urinary tract. The index has also been strengthened.

This edition discusses perfectly the fundamentals of pediatrics in a clear cut straightforward manner. It is highly recommended for students, interns, physicians and paramedical personnel, particularly nurses and social workers. If the first edition was so successful this will be more so. It is too heavy to carry in an overcoat but is the more valuable for having a more comprehensive coverage.

CONGESTIVE HEART FAILURE. Edited by Ralph M. Myerson, B.S., M.D., F.A.C.P. and Bernard H. Pastor (deceased), A.B., M.D., F.A.C.P. The C. V. Mosby Company, Saint Louis, 1967. 174 pp., illustrated. $12.85.

Reviewed by: LOUIS H. NAHUM

Congestive heart failure is one of the important problems confronting the physician. Our understanding of its pathophysiology and its therapy is now well advanced. The authors of this little book have succeeded well in correlating the fundamental disturbances present in congestive heart failure with the clinical picture and therapy.

The book is written much like a dictionary of heart failure. There are six chapters. The normal cardiovascular system, the etiology and pathogenesis of congestive failure, the diagnosis of congestive failure, the treatment of congestive failure, refractory cardiac failure and acute pulmonary edema. The cardiac lymphatics and their relation to heart failure are not considered.

The treatment of each subject is clear, precise, authoritative and yet not dogmatic. Excellent roentgenograms alongside of heart models are a real innovation and help clarify the interpretations. There are a few salt restricted diets inserted. The electrocardiograms are very few dealing with evidence of digitalis effect and changes caused by right and left ventricular hypertrophy. Prolonged bed rest in refractory heart failure is not discussed but the subject itself is excellently discussed in every other respect.

The text will undoubtedly prove valuable to students of medicine and post-graduates and practicing physicians who wish to increase their knowledge and understanding of this vital part of medical practice.

MANUAL OF PREOPERATIVE AND POSTOPERATIVE CARE by the Committee on Pre and Postoperative Care, American College of Surgeons. Editorial Subcommittee: Henry T. Randall, M.D., Chairman; James D. Hardy, M.D.; and Francis D. Moore, M.D. W. B. Saunders Company, Philadelphia and London, 1967. 506 pp. $8.50.

Reviewed by IRA S. GOLDENBERG

As modern surgical techniques become more and more complex, so also does supervision of the surgical patient before and after operation. At present, scarcely any area of human anatomy is outside the scope of reparative surgical procedures and it follows that keen appreciation of physiological aberrations is mandatory to prepare a patient for operation and to ensure uneventful postsurgical recovery. New concepts of basic body processes altered by surgical stress are reported constantly and old ideas must be discarded in light of new discoveries.

The American College of Surgeons has long recognized that many surgeons, especially those who have been in practice for a number of years, may not be cognizant of all the recent knowledge applicable to patient care. This book has been developed from a series of postgraduate courses offered by the College over the past few years to fill this gap. It is not a textbook but rather a guide in which a group of eminent surgeons present the material succinctly but completely. All the principles of current pre- and postoperative management are covered while physiological mechanisms as related to surgical patients are discussed didactically. Included are such physiological aspects as nutrition; fluid and electrolyte balance; endocrine, respiratory, cardiac and renal factors; disorders of blood coagulation; infection; and shock. In later chapters specific operations and pathological conditions are discussed without including operative technique but detailing the precepts of management of associated and induced abnormalities.

This manual serves an important function in defining what must be done by the surgeon to return his patient to health. The "how" is emphasized, but the "why" is not omitted. Any practicing surgeon or surgeon-in-training will benefit by reading it from cover to cover. As usual, W. B. Saunders has produced an excellent volume which has clear type, good page composition and a reasonable price.

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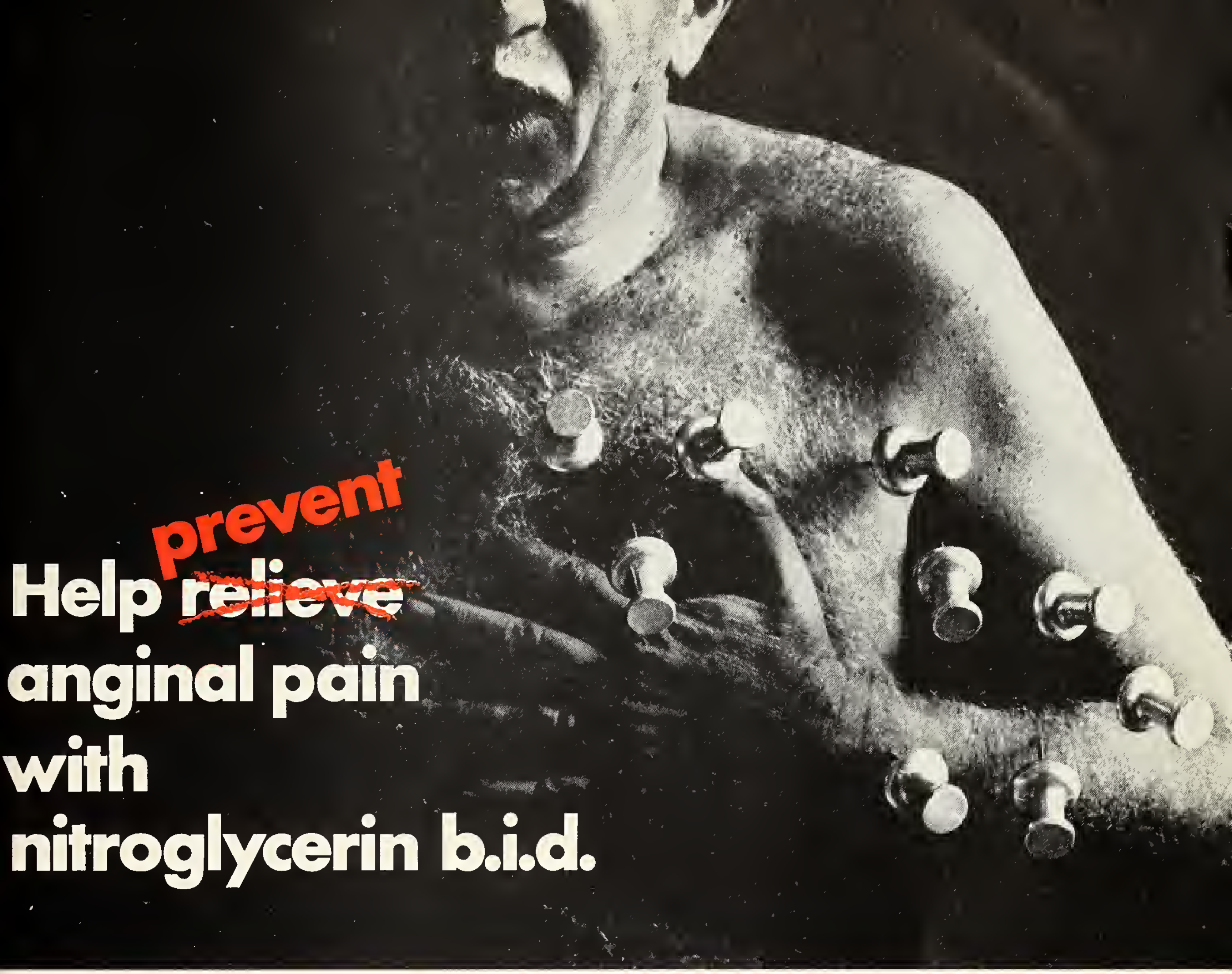

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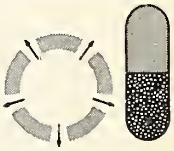

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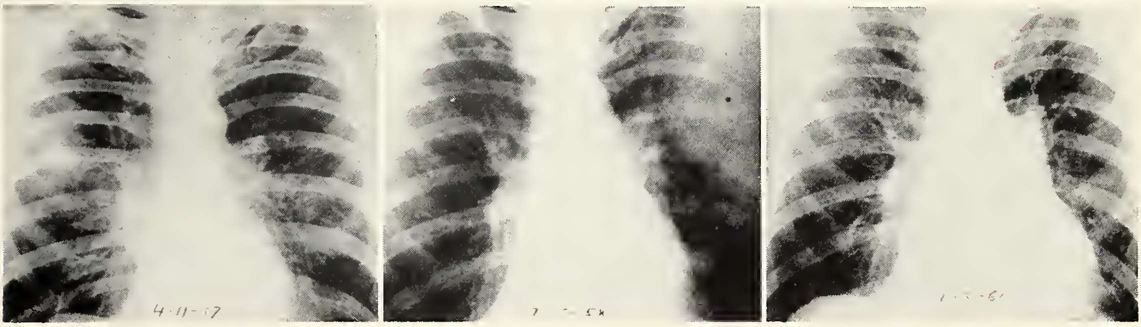

A. **B.** **C.**

A. shows an infarct on the right, oligemia on the left and plump hilar masses, B. an infarct on the left, with general oligemia, and C. the full cor-pulmonale syndrome, with a dilated right ventricle, dilated pulmonary artery and hilar arteries and oligemia of the lung.—"Recurrent Pulmonary Embolism And Cor Pulmonale"—Felix G. Fleischner, M.D., Reprinted from *The New England Journal Of Medicine,* pg. 1215, June 1, 1967.

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Connecticut Medicine

NOVEMBER, 1967
Vol. 31/No. 11

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Connecticut Medicine

editorials

Science Tools: 26. Cerebral Angiography

Failure of the cerebral circulation quickly produces anoxic function of cerebral tissue. From three to four minutes of ischemia will kill nerve cells in the cerebral cortex. In response to diminished blood flow collateral channels will develop in the neck, at the circle of Willis and over the hemispheres between major vascular channels of the brain, and between cerebral and meningeal vessels.

The physicians can no longer be content with a diagnosis of occlusion of a cerebral vessel based solely on clinical signs and a knowledge of vascular anatomy. When there is clinical evidence of cerebral ischemia the multiple factors which influence the hemodynamics of cerebral blood flow must be considered. More extensive pathological investigations and more frequent use of arteriography and more extensive surgical experience all have resulted in a better understanding of the stroke syndrome.

Many failures of the blood supply to the brain occur. There are factors in the heart, blood and arterial pressure that may play a part in producing cerebral ischemia. Then there is stenosis of carotid and vertebral arteries as well as changes in intracranial vessels within the skull. For this reason it is customary to consider the cerebral vascular tree from the aortic arch onward, since stenosis in these arteries can by interfering with blood flow have the same effect as a stenosis at a more distal site. It is for this reason that investigation of degenerative vascular disease must begin at the aortic arch and proceed peripherally. It is an implementation of this conclusion that four vessel angiography usually performed by a catheter placed in the aortic arch and elsewhere in the vascular tree has been performed.

For transient ischemic attacks or completed strokes likely to be due to infarction the first step requires an assessment of the state of the extracranial arteries. From them emboli can arise. They are the sites of constrictions which may have reduced the cerebral blood flow and they are the vessels within reach of the vascular surgeon. These vessels require visualization by an intra-arterial catheter introduced into the axillary artery and sited in the aorta. This permits good visualization of the right side of the vascular tree and two thirds of left side cases as well. In those of the left side not visualized during right catheterization the femoral route is required. There is some difficulty here because occasionally tortuosity of the iliac arteries prevents the catheter from entering the aorta. If the left carotid or vertebral shows a bruit this is the method of choice. It may even be necessary to place a needle in the left carotid artery in certain patients in whom the right axillary artery catheterization has brought the left common carotid artery under suspicion.

Every surgeon operating upon a carotid artery stenosis needs to know the state of the other side arteries including the vertebrals. Thus catheterization of the aortic arch is necessary supplemented by puncture of a single artery when it comes under question. If the clinical situation indicates that detailed study of the intracranial vessels is the preeminent requirement, then of course direct puncture of a single artery becomes preferable.[1]

There is some hazard in arterial catheterization. The most common is a thrombus at the site of the catheter puncture but this risk is very small—.06 mortality rate and 0.7 serious complication.[2] Such figures, however, are acceptable in view of the serious nature of the condition under investigation. Other lesions more rarely produced are elevation of an intra-arterial plaque and/or subintimal dissection.

Cerebral angiography is a part of a major effort to prevent strokes. It has clarified alterations in cerebral blood flow which may arise in a variety of situations. There is compression or kinking of arteries which may arise during movement of the neck especially in patients with cervical spondylitis.[3] Then there is the vertebral axillary blood diversion syndrome causing intermittent vertebrobasilar ischemia.[4] There are recurrent or completed strokes due to narrowing or occlusion of an artery in the neck. These situations can be diagnosed by angiography. As a consequence rapid serial angiography, cineflouroscopy and video tape are increasingly employed in diagnosis of cerebro-vascular disease. This multiplicity of techniques for angiography of degenerative cerebrovascular disease greatly increases diagnostic achievement and in turn our therapeutic potential.

Now that strokes increasingly afflict younger patients and the possibility is opened up by cerebral angiography that something may be done to minimize the damage already done or to prevent further damage investigation is justified. The occurrence of a transient ischemic attack in both older and younger patients is again a strong indication for investigation for this type of incident is often a forewarning of a more serious stroke which may be prevented by timely intervention.

The presence of extracranial artery bruit is a further indication for investigation as this sign increases the probability of finding a lesion amenable to surgery. It should also not be forgotten that in any series of patients presenting with a stroke, or even transient ischemic attacks a small percentage will have a cerebral neoplasm or vascular malformation. Cerebral angiography is often extremely helpful in detecting such cases as well as intracranial aneurysms.

Careful clinical assessment of the patient both as to probable site of his lesion and his general cerebrovascular and cardiovascular status is required. Then it is possible to plan intelligently the extent and the route of cerebral angiography in order to obtain the maximum relevant information with the minimum of hazard. Used in this manner, cerebral angiography undoubtedly can make a major contribution to the management of cerebrovascular disease.

L.H.N.

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Some Medical Aspects Of Drug Addiction And Abuse

A review of the records of the Chief Medic
Examiner's Office in New York City by Cherubi
showed an unusually high mortality among na
cotic addicts. The principal cause of death appea
to be sudden collapse with pulmonary edema aft
an intravenous injection. Other conditions ass
ciated with narcotic usage are tetanus sepsis, tube
culosis, hepatitis, and unknown type of chron
liver disease, endocarditis with pulmonary e
bolism, also caused by thrombophlebitis, pulmo
ary hypertension due to foreign body granulom
and complications of pregnancy. It is clear that
have been thinking hitherto about drug addicti
as a social and psychologic problem but neverth
less the clinical diseases of drug addiction are re
and require more attention on the part of phy
cians.

The significance of these disease states for i
dividual physicians and for large scale addict r
habilitation program planning is immediate a
obvious. As the current trend towards the develo
ment of a so-called "drug culture" in this count
increases, physicians will be increasingly confront
with medical emergencies and diagnostic puzzles
those who abuse drugs. Louria[2] estimates that the
are 60 to 120 thousand persons in the United Stat
who are already addicted or habituated to opiat
alone. Most of them take heroin. If we add to th
figure the thousands that use opiates illicitly, i
termittently and occasionally, the magnitude of t
problem alone becomes enormous.

Heroin addiction emerges more clearly than ev
as a life threatening and deeply hazardous existen
with a long series of gruesome complications me
tioned above. How these complications develo
becomes obvious when we view the way the addi
administers the drug to himself. The drug in t
form of morphine originates in the middle or f
east. This is then acetylated to diacetyl morphi
(heroin) in illicit laboratories usually in France
Italy. From there it is smuggled into this count
through New York City. It arrives relatively pur
but in its passage through many venal hands it
progressively diluted from 20 to 200 fold by bei
mixed in egregiously unsterile fashion with quini
lactose mannitol or even baking soda.

After the street vendor (pusher) sells the one
five per cent heroin to the user, the latter mixes th
powder with unsterile water, heats the mixtu

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briefly in a spoon or bottle cap with a match or lighter, then draws the heroin into a syringe or eye dropper through cotton to filter out the larger impurities. The heroin is then injected intravenously without any attempt at skin cleansing. The user commonly injects the heroin in the presence of one or more fellow users in the group, often sharing the needle without any attempt at sterilization between the intravenous inoculations. It is small wonder that self-administered opiates in this fashion produces severe medical complications which include overdose, pulmonary infections, bacterial endocarditis, hepatitis, cellulitis thrombophlebitis, and tetanus.

Overdose kills one per cent of users every year. In 1964, 380 overdose deaths were recorded. The overwhelming majority of users experience overdose at least once because of the variability of content of the heroin packet. The increasing venality of traffickers in narcotics will result in greater unpredictability as to exact dose and thus present the heroin addict with ever increasing risks of inadvertant overdose. However, there are more to the clinical findings in "overdose" than just excessive amounts of heroin injected. Many a typical instances of sudden coma and pulmonary edema, suggest allergic reactions, histamine release and poison by toxic adulterants. For this reason nalorphine (nalline) while usually beneficial is occasionally difficult to titrate against heroin dose and may be variable in its effect or unpredictable.

Perhaps the greatest interest that attaches to Cherubin and Louria's reports have to do with the implications on the broader perspective of the possible consequences of the spreading use of all psychedelic agents for purposes once reserved for alcohol. Just as in the case of heroin we can expect a steadily increasing number of adverse reactions will be uncovered in various endemic centers of drug abuse, and new complications will be identified also. For example LSD, the mind expander, has now been shown to have deleterious influences on chromosomes of leucocytes in cell culture.[7] In the patient, Frosch reports, LSD produces acute reactions of either a panic or a psychotoxic type of overwhelming anxiety, fear of "going crazy" a sense of helplessness and loss of control. The psychotoxic reaction is one of paranoia, confusion or brave responses to grandiose or persecution delusions. Finally is the recurrent reaction or the spontaneous return of feelings felt under the influence of the drug which occurs in about a third of those who take LSD and may occur up to a year after the actual experience of the drug.[3,4,5]

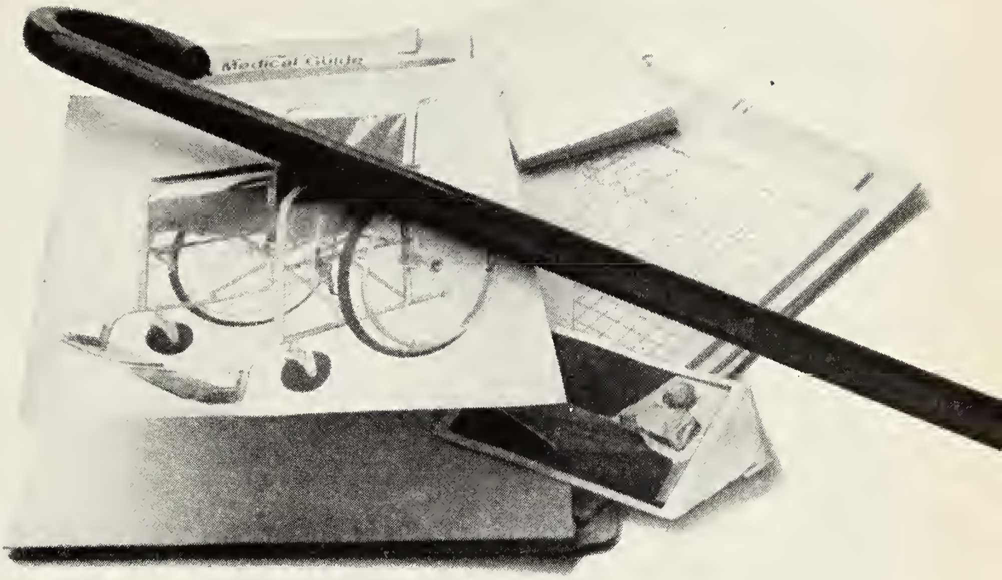
Now we are beginning to hear that intravenous injection of amphetamine has become a well established and extensive form of drug abuse all over this country. Recently Federal agents on Long Island seized a fifty pound shipment of amphetamine powder worth 1.75 million dollars and again in Chicago. The drug is also injected intravenously and the user experiences a sudden overwhelming pleasurable feeling called a "flash" or a "rush" immediately after injection. The user remains awake continuously until he becomes so exhausted, disorganized, tense or paranoid that he ceases using the drug and goes to sleep. The toxic reactions users experience are abrupt and extreme mood changes, frightening images, extreme sensitivity to sensory stimulus, belligerance sometimes to the point of violence and severe paranoia. Other side effects are weight loss, occasional severe chest pain and unconsciousness following an overdose. Ultimately memory and ability to concentrate are permanently impaired.

It is clear that drug abuse is widespread. We must be alert to identify adverse reactions as soon as possible and this includes the chronic sequelae as well as the acute syndromes. A serious suspicion has already been raised with regard to chronic liver disease in heroin cases. But there are many other possibilities and the proportion of all drug abusers who finally develop some type of chronic disability may prove to be considerable just as it is already clear that narcotic addicts are highly prone to disease and death.

Information presently at hand does have great significance with regard to what is likely to be the need for medical care in drug addicts. Since drug deaths seem to be concentrated in certain deteriorated neighborhoods, our need is to cure slumism. Then there is the need for providing continuous medical supervision with associated in patient services. Finally is a requirement for medical screening procedures which must be devised to identify those addicts affected by the associated disease states or who run a high risk of developing them. Obviously an addict treatment program that incorporates these three enlightened approaches can claim that they are approaching good prevention and treatment of drug addiction.

In any case it is now abundantly clear that the increasing misuse and abuse of drugs poses grave medical as well as social problems to today's society.

L.H.N.



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Electrocardiographic Paradoxes

The electrocardiograph is a precision instrument. It does not err. When errors are made they are made by the interpreter who should know more, but who should diagnose less, leaving room for the clinical picture and the doctor to make the final diagnosis. In other words in the scheme of a diagnosis the electrocardiogram can play an important role, but an electrocardiogram is not the doctor.

Errors that can be made when this concept is not taken into account are numerous.[2] Likoff and his co-workers[1] described six young men asymptomatic and vigorous who were sent for examination because of heart murmurs. Their electrocardiograms showed changes indicative of myocardial infarction. However, the most intensive work-up including coronary arteriograms failed to reveal any other evidence of cardiac much less coronary artery disease. The paradox incidental to the discovery of the electrocardiographic pattern of myocardial infarction in patients who are otherwise well was resolved not alone by coronary arteriography which makes visible the larger coronary vessels and leaves out the minute vessels, but by the physical examination. The patients were young, vigorous, and no cardiac enlargement or myocardial inadequacy. In short Likoff's patients revealed that a pattern of myocardial ischemia, injury and necrosis may appear in normal young individuals.

The commonest disturbance in the heart to produce a wide Q is myocardial infarction and when taken in association with elevated ST segments this pattern in the electrocardiogram represents the most reliable criteria for the existence of myocardial infarction. However, a large number of other common and uncommon conditions also write sizeable Q waves in the tracing and can provide a troublesome source of diagnostic confusion. Marriott[2] describes a patient who was admitted for myocardial infarction who showed a large Q wave and inverted T which turned out to be an artifact arising from reversed electrodes. At times STT patterns alone especially when accompanied by chest pain can be confusing enough to lead to a confident diagnosis of infarction. And yet we know that STT displacements may be merely unrecognized normal variants. The kind of dislocation of normal lives which such errors can produce may be considerable.

The main mimics of myocardial infarction, however, are these conditions that produce persistent Q. waves. They can be found in localized myocardial replacement by fibrous scar, in diffuse myocardial disease, in ventricular hypertrophy, in extracardiac catastrophes, in pre-excitation as well as unknown causes as was noted in Likoff's patients.[4, 5]

In localized myocardial replacement one has normal muscle interspersed with inert scar tissue much as one finds in myocardial infarcts. These scars have the same effect upon the electrical forces. So do infiltrates of leukemic, sarcoid, amyloid and metastatic origin distort early depolarization with development of Q waves.

Not only localized deposits of abnormal tissue can distort the initial electrical forces but diffuse myocardial processes can also produce Q waves and simulate infarction. Such involvement are legion and include scleroderma, various idiopathic cardiomyopathies, acute myocarditis, glycogen storage disease, amyloidosis, Friedreich's ataxia, pseudohypertrophic muscular dystrophy and many others. Diffuse thinning of the left ventricular wall as a result of the anomalous origin of the left coronary from the pulmonary artery can mimic an acute anterolateral infarction to perfection.

Any condition that leads to ventricular hypertrophy may result in the loss of precordial R with development of QS complexes in certain leads. This may suggest infarction in the minds that have too much respect for Q. waves per se. These Q. waves can disappear if leads are taken at a lower level where they asume an R wave in absence of infarction. Similarly diastolic overloading, as well as idiopathic hypertrophy and subaortic stenosis often lead to sizeable Q. waves in limb and chest lead.

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extent that infarction pattern can appear in the electrocardiogram. Several examples of acute pancreatitis have been published with an ECG pattern indistinguishable from infarction although at postmortem no sign of coronary artery disease was present. Similarly cases of pneumonia complicated by circulatory collapse, revealed ECG supposedly diagnostic of MI yet at autopsy there was no sign of infarction. Acute pulmonary embolism often produces o Q3T3 pattern that simulates inferior wall MI.

Several types of Wolff-Parkinson-White preexcitation are reported by Marriott that mimic myocardial infarction in every region of the myocardium. This mimicry can usually be exposed by noting the other hallmarks of the syndrome such as short p-r interval, typical delta waves in other leads and absence of associated STT changes typical of infarction.[6]

It is obvious that those who have responsibility to report on the ECG must become familiar with the multitude of coronary mimics so as to avoid doing a disservice to patients with normal heart by stigmatizing them with a coronary label. Further, if we fail to recognize that abdominal catastrophes can simulate acute myocardial infarction in the ECG, we may be responsible for staying the surgeon's needed scalpel and lose a life.

Because the electrocardiograph is a precision instrument, physicians in search of an exact diagnosis may be inclined to depend too much on an electrocardiographic diagnosis. The example mentioned above show that the ECG is not a doctor and that it is the doctor who must evaluate the overall clinical picture and make the diagnosis being aided by all needed laboratory devices of which the electrocardiogram is an important one.

L.H.N.

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Use Of Defoaming Agents In Acute Pulmonary Edema

In pulmonary edema, fluid from the blood infiltrates the thin structures of the lungs. It then seeps into the alveoli and bronchioles. Because of the physical characteristics of the fluid which contains a relatively high protein content and because of the to and fro movement of air, bubbling at some point necessarily occurs. Once this occurs there is an expansion of the initial mass of fluid with serious impairment of air exchange. Thus several stages follow each other, edema, exudation foaming and asphyxiation either partial or total.

The diseases in which pulmonary edema occurs are many, varying from diseases of the lungs or the heart, of the brain and in allergic states. Even healthy subjects can develop pulmonary edema at very high altitudes. Among the cardiac diseases we find pulmonary edema occurring in paroxysmal hypertension, shock, myocardial infarction and mitral stenosis. Among the brain disorders pulmonary edema occurs in trauma to the skull, strokes and lesions near or around the third ventricle internal capsule and the lenticular nucleus.

Pulmonary edema, from whatever cause, starts a vicious cycle of events which tend to prolong the attack. The cycle is based on high pulmonary pressure, transudation and accumulation of fluid in the alveoli, foaming resulting in hypoxia which in turn leads to more transudation, more foaming and more hypoxia. Obviously it is necessary to treat the underlying fault. If there is too much venous return it must be reduced. If there is a failing heart its contractile force must be improved. The congestion in the lungs must be rapidly reduced and hypoxia must be combatted. This seemingly rational approach, however, has been hampered by tradition and erroneous concepts for what may be helpful in one situation may be harmful in another.

Decreasing the venous return can be accomplished in several ways. Tourniquets on the legs and arms will reduce blood return to the heart and prevent overloading of the lungs. Compression of carotid sinuses will inhibit sympathetics, slow the heart and produce peripheral vasodilation and also reduce venous return. A small dose of morphine will reduce restlessness, reduce pulmonary artery constriction and prevent further exudation into the alveoli. Rapidly acting diuretics formerly mercurials and now ethacrynic acid and furosemide will reduce blood volume, venous return and also aid in reabsorption of fluid from alveoli.

If left ventricular failure is present then rapidly acting digitalis preparations such as digoxin, cedilanid or ouabain is immediately indicated to improve left ventricular contractile force and increase cardiac output. However, if the cause of pulmonary edema is a very tight mitral stenosis, digitalis would be contraindicated, since it could increase the output of the right ventricle and further flood the lungs and aggravate pulmonary edema.

Procedures which tend to lower pulmonary capillary pressure are most effective in those instances in which there is a high arterial pressure, rapid circulation time, increased cardiac output and a rise in pulmonary pressure. However, they can be dangerous if employed in severe mitral or aortic stenosis, inhalation of toxic gases or severe pulmonary embolism.

Hypoxia may occur in pulmonary edema either as a primary or secondary factor and the use of O_2 is a rational procedure. Originally oxygen was used only in subjects with pronounced cyanosis. However, hypoxia itself is a possible factor in causing or aggravating pulmonary edema since it causes pulmonary veno-constriction and systemic venoconstriction. Its relief would seem to be truly an essential aim in therapy. Moreover clinical improvement follows its use in many cases. Unfortunately when foaming occurs in the bronchioles this prevents oxygen from reaching many of the alveoli. Ordinarily 100 per cent oxygen is administered in a humidifier in order to prevent drying of the mucosa. But oxygen in high concentration is an irritant and its administration needs to be interrupted by periods of normal air breathing.

We must remember that large amounts of fluid may be present in the air passages with little danger to life. However, as soon as the surface tension reaches a critical point foaming starts. This leads to extremely severe effects, partly through enormous increase in volume and partly through modification of the normal alveolar function which is based upon surface tension effects between the humid alveolar surface and air. Since impairment of the normal gas exchange of the lungs is followed by hypoxia which causes pulmonary venous constriction

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L.H.N.

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Delayed Dermal Sensitivity In Recipients Of Inactivated Measles Virus Vaccine

One of the recommended technics of vaccination against measles is to give a course of killed measles virus followed after an interval of months by a booster of attenuated measles virus either accompanied or unaccompanied by gamma globulin.[1] This technic was advocated to prevent untoward reactions that may accompany the administration of live virus even when gamma globulin is given coincidentally. However, in a certain number of these children a local and sometimes general reaction may follow the final inoculation of the live virus vaccine whether or not an accompanying dose of gamma globulin is given. The reaction consists of erythema at the site of injection within twenty four hours, fever for six days, a wheal-like lesion lasting one month and induration for four months.[2,3] If hydrocortisone is given for twenty four to forty eight hours the illness is shortened dramatically.

The mechanism of the reaction suggests an Arthus-type reaction in a sensitized person.[4] The killed virus seems to sensitize some patients in a way that live virus cannot. Others have reported this phenomenon also.[5] Children previously inoculated with killed measles virus, when they develop natural measles may show serious consequences in the form of urticarial, vesicular petechial, rashes, swollen hands and feet, and erythema multiforme. Whether the mechanism of this reaction is due to virus antigen or an element of the media in which the virus was grown, its occurrence is a serious drawback to the use of the killed measles virus for routine immunization.

Lennon et al[6] investigated skin test reactivity to measles and polio-virus antigens among children who had previously received inactivated measles vaccine. He found a surprisingly high incidence among recipients of killed measles vaccine of delayed dermal hypersensitivity to antigens found in both inactivated measles and polio-virus vaccine. This sensitivity was not found among children who had received live attenuated vaccine or who had recovered from the natural disease. Which components of the killed preparations may have served as the sensitizing agents is not known, but the reactivity to polio-virus vaccine also means further study is necessary to determine what element in the vaccine it is that is responsible for the hypersensitivity.

It is very possible that similar sensitizations may have been provoked by other killed vaccines. This suggestion has arisen in clinical studies of inactivated antigens prepared from the respiratory syncitial virus mycoplasma pneumoniae and the trachoma agent.[6] These may eventually prove to be unrelated in etiology, but until the pathogenesis in each case has been further clarified, a further element of caution must be added in the consideration of these and any other new inactivated vaccines.

In the specific case of killed vaccine for measles, it seems justified to discontinue its general use. This recommendation is really not stringent because inactivated measles vaccine fails to confer enduring immunity against measles anyhow. All individuals who have received killed virus vaccine are now suspect and continuing surveillance of such groups is fully justified. Simultaneously further studies with laboratory models will undoubtedly be stimulated in order to delineate the cause of such events and to prevent their occurrence.

When a severe reaction does occur in recipients of killed measles virus vaccine when they are inoculated with attenuated virus or when they acquire the natural disease, McNair's experience with the gratifying results from the use of hydrocortisone needs to be borne in mind.[2]

L.H.N.

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Desiccated Thyroid vs. Synthetic Thyroid Preparations

There is a variation in potency and hormonal constitution that may occur among thyroid preparations from the same source or different animal species. Some of these variations are due to seasonal and geographic factors. Others are due to species differences. For example porcine thyroid preparations have significantly more goitre prevention activity than those prepared from a bovine source. Then there are differences in methods of processing or other as yet unknown factors. Finally there is the question of hormonal stability upon prolonged storage. As a result there are impotent or weakly potent preparations despite conformance with US Pharmacopoeia requirements.

It is now known that there are four iodine preparations in the thyroid gland, monoiodotyrosine, diiodotyrosine, l-triiodothyronine (l-T3) and l-tetraiodothyronine (l-T4) or thyroxine. The thyroglobulin in thyroid consists of 80 to 85 per cent of the first two which are calorigenically inert and only 15 per cent is l-T4 and l-T3. So that total hormonal activity is dependent on l-T4 and l-T3. l-T3 is approximately four times as effective orally as is l-T4 in maintaining the euthyroid state. Therefore, small variations in the quantity of l-T3, which is no more than one fifth of the total quantity of active hormone will account for relatively large changes in hormonal activity. The small amounts of l-T3 involved are not sufficient to alter the serum PBI. even when l-T3 is in excess.

The serum PBI. level on replacement doses of thyroid is dependent instead not on the quantity of l-T3 but on amount of l-T4 present. If l-T4 is low one can have a PBI. level disproportionately low compared with the patients metabolic status. In contrast if some desiccated thyroid preparations are devoid of l-T3, the l-T4 present could keep the PBI. normal and still the preparation could be clinically inert. This is the reason why pharmacopeial standards for total iodine content do not offer a reliable guide as to the therapeutic potency of the desiccated thyroid preparations. That marked variations in the content of l-T4 and l-T3 in desiccated thyroid preparations, actually do occur has been well documented by Selenkow and Wool.[1]

The synthetic l-T4 and l-T3 have been commercially available for over a decade. Each has received widespread acceptance and both are in daily use throughout the world. Neither alone simulates all the metabolic characteristics of endogenous thyroid gland secretion. l-T4 has a slow, gradual onset of action, is incompletely absorbed when taken by mouth and produces PBI. levels in serum that are disproportionately elevated compared with the metabolic status of the individual. On the other hand l-T3 has a brisk, short-lived action, is well absorbed by mouth, but fails to raise serum PBI. levels in physiologic replacement dosages. It seems logical, therefore, in view of the inadequacies in standardization of animal thyroid, that an appropriate blend of synthetic l-T4 and l-T3 would be desirable.

A mixture of 90 per cent l-T4 and 10 per cent of l-T3 was suggested by Taylor.[2] However, this preparation would give disproportionately high levels of serum PBI. because of its high content of l-T4. Selenkow and Wool now report on their combination of 80 per cent l-T4 and 20 per cent l-T3 in 57 patients with primary myxedema, six with pituitary myxedema, groups of non toxic goitre patients, normal and goitrous pregnancy, hyperthyroidism treated with a combination of antithyroid drugs plus thyroid hormone. They employed this combination of 4:1 by weight because it simulates the metabolic effects of endogenous thy-

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Adverse Reactions: The most common are nausea, edema and drug rash. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Mild drug rashes frequently subside with reduction of dosage. However, rash accompanied by fever or other systemic reactions usually requires withholding medication. Purpuric rash has also been reported. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

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*Stein, I.D.: Presented at the American Academy of General Practice, Dallas, Sept. 1967.

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roid hormone secretion. The combination of 3:1 is thought by some to be more nearly physiological.

In the myxedematous patients the hormone combination produced a level of PBI. and other thyroid parameters which were representative of the patients metabolic status. The combination was well tolerated within a wide therapeutic range. There was a modest increase in PBI. over that found with desiccated thyroid, but it was not possible on clinical grounds to differentiate between those patients on a comparable equal calorigenic dose of the natural or the synthetic preparations. An extra dividend came from their studies of thyroid function in pregnant women and their infants at term. They found that the maternal and fetal circulation contain the same amount of thyroxin at term. This suggests that exogenous thyroxin given to women during pregnancy could contribute significantly to fetal thyroxin levels and would thus provide adequate replacement for any inadequacy of fetal thyroid secretion.

It has been many times emphasized that the ultimate determination of "clinical euthyroidism" rests upon the patients subjective evaluation of well-being as well as the physician's experience in making this appraisal. Neither the B.M.R. nor the more objective laboratory parameters of thyroid function—PBI. resin T3, "free thyroxin" are of sufficient specificity or reliability to be used without reservation to assess the full effectiveness of thyroid hormone therapy. At best they are useful guides for assisting the physician in determining achievement of clinical euthyroidism. The correlation of PBI. levels and thyroid dosage on Selenkow's study do not necessarily indicate a direct measure of the desired clinical effects. Good judgment must still be exercised in interpreting PBI. and resin T3 values as indicating "euthyroidism." A laboratory test cannot substitute for the clinician.

The synthetic combination used by Selenkow and Wool can be used for clinical purposes in the same manner as comparable dosages of desiccated thyroid. However, the thyroid function tests appear to be more consistently indicative of the clinical thyroid status when the synthetic combination is used, than when synthetic hormones are each used alone or animal thyroid preparations are used. It is not necessary at this point to point out the precautions that should be considered when the synthetic hormone combination is used in the elderly, in patients with adrenocortical insufficiency and in patients with known or potential cardiovascular disease, precautions that apply equally to all thyroid preparations.

From the numerous studies of synthetic thyroid hormones used separately and from the results reported by Selenkow and Wool, it seems justified to conclude that the combination of l-T4 and l-T3 in a ratio of 4:1 by weight is an effective hormonal preparation for clinical usage. It has the advantage of chemical purity obviating the need for either analytic or biologic standardization and in addition it simulates the clinical and metabolic actions of endogenous thyroid gland secretions. It should find a useful place in the treatment of all thyroid disorders requiring hormonal therapy.

L.H.N.

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Percussing Bones: Electroacoustic Analysis Of The Skeletal System

If one strikes the anterior tibia with a percussion hammer in a single quick blow one produces a sound. In young people this sound resembles a musical sound or tone. In an elderly subject on the other hand the sound has more of a cracked-pot quality. It is known from clinical experience that similar changes of quality can be heard in the percussion sound obtained from the human skull in Paget's disease, in metastasizing cancer of the prostate and in multiple myeloma. The sound elicited by percussion of the tibia in generalized osteopathies displays certain differences from that elicited from normal bone and these differences can be detected by ear after a little practice. It means, of course, that we must begin to percuss bone and become familiar with changes encountered much as we have learned differences in percussion sounds of lungs and heart. Apparently the differences in bone sounds elicited by the percussion hammer are not affected by the length of the bone or the force of the blow, but rather reflects a constant in the bone material depending on its structure and hydroxyapatite content.

Since the judgment of auditory phenomena is likely to be affected by subjective factors, percussion sounds cannot be usefully compared during the treatment of generalized osteopathies. In order to place recording of sounds on an objective basis the devising of an instrument for this purpose seemed a logical step to take. Freyschmidt has devised such an instrument and termed it an electro-acousto-spectrograph. His method consists of placing on the crista anterior tibia a cast iron shell designed as a sound proof chamber having a rubber edge which fits snugly on the skin. Inside of the chamber is a microphone which records the sound waves on an endless magnetic tape. A blow is struck by a percussion hammer on the tibia a handbreadth away from the microphone. The sounds which are recorded are then analyzed with the aid of a frequency analyzer and registered by a constant voltage write-out system.

If one maximum oscillation is recorded in the analysis of the percussion sound the acoustic impression will be a tone. If there are several secondary maxima which are integral multiples of the fundamental oscillation, then a musical tone is perceived. If there is no integral relationship between the secondary oscillation and the principal maximum then acoustically a noise is heard. Apparently the length of the bone or the tissue over it do not alter the nature of the sound and it is this fact which allows comparison of oscillatory spectra. One finds that the results are reproducible, consistent, and accurate.

Percussion of the tibia of a normal skeleton produces a musical sound or tone. In young people the sound is musical whereas in the elderly subjects it was more often a noise. A striking finding was the pronounced difference in the frequency spectrum of the right and left leg and this Dr. Freyschmidt believes is due to a difference in their hydroxyapatite content the greater the amount of this material the more musical is the tone. This, of course, means that frequency spectra should always be recorded for both tibia.

Freyschmidt reports on 58 spectrograms of patients with generalized osteopathies and found a distinct numerical shift from musical sound of normal bones to noise in diseased bones. The osteopathy bones also showed a difference in tone between the right and left tibia. It will be of particular interest to determine the efficiency of electro acoustic analysis of the skeletal system as a means of following the course of generalized osteopathy. X-ray procedures can detect changes in content of hydroxyapatite only of the order of 30 per cent with any certainty and this makes this technique too

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insensitive a procedure for evaluating results of treatment.

Freyschmidt quotes the case of a patient of 72 with osteoporosis treated intensively for one year. The X-ray revealed no change, but the pain in the bones had subsided and the acoustic spectra had changed from a noise to that of a tone. Further series of tests are being performed in a variety of patients some with osteoporosis, others with osteomalacia, hyperthyroidism and parathyroid disorders in order to determine the useful range of sensitivity of the electro acoustic process in diagnosis and the evaluation of therapy as compared with standard X-ray procedures and quantitative roentgen determination of the calcium content of skeleton.

In the meanwhile we can all begin to percuss bones and become familiar with variations in tone that occur in health and disease. It will sharpen our clinical appraisal of the skeleton.

L.H.N.

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What We Can Learn From An Analysis Of Cases Of Sudden Death

Much thought and effort is being devoted to construction and proper use of the coronary care unit. Its purpose of course is to save lives that would otherwise have been lost without immediate resuscitation. This is accomplished by monitoring the patient from the time of admission and by being prepared to treat the patient for the life threatening arrhythmias during the critical period of the first three to four days. Saving lives by successfully combatting cardiogenic shock has not been so rewarding as is the control of arrhythmias. In addition to monitoring and treating the patient during the critical period the coronary care unit provides facilities for research into the prevention of serious cardiac complications. Furthermore, increasing experience in this field should show ways of achieving similar results with greater economy of personnel and apparatus.[1, 2]

Despite these advances in treating the patient with acute myocardial infarction there remains the startling fact that these treatment methods are effective only after an individual reaches a hospital and lives during the first twenty-four hours, whereas there are 66.8 per cent of patients who are either dead on arrival or die outside the hospital.[3] Only 12.2 per cent of deaths occur in the patients admitted with acute myocardial infarction who have survived the first twenty-four hours in a hospital. Any treatment which is effective only after an individual reaches a hospital will therefore have little effect on the total mortality from arteriosclerotic heart disease (ASHD) unless we understand how to diagnose and save the patient with minimal symptims who then goes on to sudden death, since as we have seen from Kuller, Lilienfeld and Fischer's report[3] 66.8 per cent of ASHD died suddenly.

It would seem that at present methods to prevent development of ASHD as well as early recognition are much more likely to have a demonstrable effect on coronary artery disease mortality than the therapeutic methods that depend on the individual surviving at least twenty-four hours in a hospital. This in no way denies the value of the life saving measures to the individual who enters a hospital and is saved by various types of resuscitation.

Routine vital statistic reports indicate that approximately 80 per cent of ASHD deaths occur in a hospital, an estimate based on a statement on the death certificates of Baltimore City. This seems to suggest that improvement in treatment of such patients could significantly reduce total coronary artery disease mortality. However, a more intensive review of the survey of events surrounding such deaths clearly indicate that a large proportion of such deaths, the patients were either dead on arrival (55.2 per cent) or dead within twenty-four hours after admission (18 per cent). It would seem therefore, that the potential benefits of hospital treatment in terms of influencing total cardiovascular mortality may be more limited than we think.

With respect to the possibility of the reduction of ASHD mortality in the forty to sixty-four age group, several important facts were reported by Kuller and his co-workers. First of all is the striking fact that 60 per cent of deaths attributed to ASHD were sudden and that only 18.9 per cent of the individuals who died from ASHD in Baltimore City survived longer than twenty-four hours in a hospital and even of these latter one-third had been previously admitted with a different diagnosis.

A further analysis of those who died suddenly from ASHD, 50 per cent had a history of heart disease diabetes or hypertension and a quarter of them had seen a physician within a week prior to death. Only 90 of the total 1,098 deaths from ASHD had either occurred within two hours or were unwitnessed among the persons who did not have a history of diabetes, heart disease, hypertension or stroke and also had not seen a physician within a month prior to sudden death. This means that in these eight per cent careful medical diagnosis was not possible and these patients could not have been saved. In such patients only primary prevention could have been effective in reducing the mortality.

Of the remaining patients with sudden death somewhat less than half had seen a physician recently and over half with a history of ASHD, diabetes, hypertension one could suppose that both primary or secondary prevention might be effective. If we reduce the incidence of new ASHD in white males, fifty to sixty-four, by 20 per cent, it would have reduced the total mortality by 20 per cent. The importance of this figure becomes plain when we consider that a new treatment that would be effective after the first twenty-four hours of hospitalization would have to save every patient to produce a similar reduction in mortality, an obvious impossibility.

This points up the importance of better diagnosis and case finding before the acute attack of ASHD. It will be noted above that over one-fourth of the cases of sudden death had seen a physician a week prior to death and that relatively few had not had medical care within a period of about six months prior to death. Did such patients require improved diagnosis, did they shirk their individual responsibility to carry out the doctors orders or is the disease relentless, and death inevitable regardless of medical intervention. We would all like to believe that this third possibility is not true. In any event such studies are urgently needed fully as much as are improved therapeutic methods that may prevent fatality.

L.H.N.

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Control Of Cancer By Endocrine Methods

The natural course of cancer is very different in various types of malignant disease. Some tumors grow without any restraints whatever and death may ensue in say six weeks. Other malignant growths disappear spontaneously. Both of these antipodal effects are rare. Some patients with cancer live one year or longer after the neoplasm becomes manifest and it would appear that some inhibition of growth of the tumor takes place to produce this retracted course. Of the many factors that restrain cancers, the endocrine status of both tumor and host is the one to which Huggins devotes much of his time and his important contributions were basic enough to be recognized by the Nobel Committee.

The proof that hormones can influence the growth of cancer was derived from tumors of the prostate in aged dogs and later in man. After orchiectomy the prostate shrinks, oxidative phase of carbohydrate metabolism declines and prostatic secretion stops. Testosterone corrects these defects. Thus one can achieve a cycle of growth and atrophy by providing and withdrawing testosterone. In the absence of testosterone the prostatic cell shrivels although it does not die. The prostatic cancer cell is entirely different. It grows in the presence of supporting hormones but it dies in their absence. For this reason it cannot participate in growth cycles. Even prolonged starvation will not prevent prostatic cancer growth in the presence of testosterone.

Measurements of phosphatases in blood serum furnished proof that cancer of the prostrate in man is hormone responsive. The prostate of the adult human male is rich in concentration of acid phosphatase. When prostatic cancer metastasizes large amounts of acid phosphatase are produced and significant increases in acid phospatase are found in blood serum. Prostatic cancer frequently metastasizes to bone where osteoblasts give rise to increased alkaline phosphatase activity in the serum. Changes in these enzyme measurements gave accurate information whether orchiectomy caused regression of cancer of the prostate, whereas testosterone enhanced growth rate of the neoplasm and caused increases in the acid phosphatases, if growth involved non-bony tissues, and increased alkaline phosphatases if growth involved bone.

A similar model was found in fibrinolysin levels in the blood. Human prostatic fluid contains large amounts of many fibrinolysins which are especially active against fibrin. This explained why patients who have metastatic cancer of the prostate have blood which is incoagulable. But it also offered a method of studying development and regression of prostatic cancer since proteolytic enzymes of the blood rise with growth of the cancer and fall with hormonal therapy. Obviously a patient with high proteolytic activity of the blood should not be subjected to orchiectomy but should receive diethylstilbestrol instead. The significant point is that each enzyme, phosphatase or fibrinolysin enters the blood only when metastasis have taken place and their absence is evidence of localization of the tumor in the prostate.

With regard to mammary cancer, it was found that the testes can support the growth of mammary cancer in the male. The hypophysis and the adrenals can support mammary cancer in the female. In some women with mammary cancer the growth thrives even though they have no ovarian function, whereas in others, regression of great magnitude can occur with administration of phenolic estrogens. A paradox was here uncovered. In some circumstances estrogenic compounds are activating agents for breast cancer, while in others estrogen lead to a therapeutic triumph. This vexatious paradox was resolved by experimental studies when it became possible to produce cancer in rats by aromatic hydrocarbons.

In the male rat mammary cancers induced by aromatics were not influenced by orchiectomy or hypophysectomy — they were not hormone dependent. By contrast most mammary cancers of men wither impressively after deprival of supporting hormones. In female rats similarly the mammary cancer caused by aromatics was hormone responsive. Many though not all induced mammary cancers vanished after removal of ovaries or pituitary. It is obvious that both man and animal can have some of their cancer cells which are hormone dependent while other neoplastic cells in the same organism are not endocrine-responsive. It seems to be a basic proposition in endocrine-restraint of malignant disease that cancer cells can differ in a crucial way from the ancestral normal cell in response to modification of the hormonal "milieu interior" of the body.

What was unexpected was the finding by Huggins that mammary cancer in the female rat can be extinguished by providing excessive amounts of ovarian steroids, a form of control by hormone interference. He induced mammary cancer in rats which were then treated for a limited time with large amounts of estradiol and progesterone. In normal animals this combination excites excessive growth of the breasts. In cancer animals this combination cures over half of their tumors and they do not reappear. This same observation was carried over to the treatment of patients with mammary cancer in both men and women with far advanced disseminated disease in whom large amounts of progesterone and estradiol were injected intramuscularly. Worthwhile improvement was obtained in many patients.

There is another kind of hormone interference based upon the classic observation of Dougherty and White in 1943 that ACTH causes lysis of lymphoid cells. Glucocorticoids can cause a remission of some chronic lymphogenous tumors, leukemia, Hodgkins.

The control of cancer by endocrine methods can thus be described in three propositions: (1) "Some types of cancer cells differ in a cardinal way from the cells from which they arose in their response to change in their hormonal environment; (2) Certain cancers are hormone dependent and these cells will die when supporting hormones are eliminated; (3) Certain cancers succumb when large amounts of hormones are administered."

L.H.N.

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Pathogenesis Of Duodenal Ulcer

Patients with duodenal ulcer are often described as chronically anxious which implies an emotional factor. What is the role of emotion and conversely do gastric symptoms cause emotional states? Clinical observations do support the concept of a psychosomatic etiology in a significant number of cases and serious students of duodenal ulcer do not disagree with this idea. Also there remains to be clarified the mechanism by which emotional experiences produce or exacerbate ulcer disease. Obviously if we had the knowledge of the mechanisms it would be of great aid in the control of the factors concerned.

There are two pathways connecting the brain and the stomach over which emotional factors could operate—the nervous and the neurohumoral. The nervous pathways are through the autonomic nerves both vagus and sympathetic to the upper gastrointestinal tract. The neurohumoral pathways are via the hypothalamus, pituitary and adrenal glands. Under the impact of emotional stress the impulses could pass down the vagal fibers and activate the secretory functions of the stomach. Over the sympathetics, impulses could constrict the blood vessels to the duodenal mucosa and reduce its nourishment. It is hypothesized that this could make it susceptible to the damaging action of acid in the stomach. Activation of the adrenal cortex by the neurohumoral route has been proposed as an intermediary mechanism in ulcer genesis. This could lead to release of corticosteroid hormones which might stimulate gastric secretion or else impair the secretion of mucus or by some as yet unknown mechanism.

The evidence in support of these theories is far from complete. In the first place, the amount of investigation carried out on subjects has been quite scanty considering the importance of the problem. When we consider the complexity of the research involved it is understandable why the research has been scanty. To acquire necessary data, a large number of duodenal ulcer patients as well as a large number of controls would have to be monitored continuously through out their daily activities with portable equipment, that could record such functions as the intra-duodenal acidity, motility and mucosal blood flow.

If emotions produce ulcer they must do so by influencing the stomach, duodenum and perhaps the pancreas. Until the present most of the attention has been directed to the stomach especially to the role of acid and pepsin secretions which are easy to measure. In this way it was found that no case of duodenal ulcer has ever occurred in the presence of achlorhydria. From this has arisen the conviction that acid secretion of some degree is essential for the development of duodenal ulcer. It is equally clear, however, that acidity cannot be the sole factor since many cases occur in whom acid secretion is low and many patients reach the fourth and fifth decade of life with a very high acid output and yet have not developed a duodenal ulcer. An extreme example is the patient with Zollinger-Ellison syndrome who secretes a very high amount of acid per hour and in whom ulcer cannot be demonstrated.

There is, however, a limit to the amount of acid the duodenum can withstand without some damage. This has been demonstrated in animals. The only point is that the damage consists of widespread inflammation and erosion without focal ulceration. To explain the localization of duodenal ulcer we must perforce invoke further factors of a mechanical impact. This means that the antro duodenal anatomy be of such a kind that the emerging acid impinges upon a circumscribed area of the duodenal bulb and eventually erodes the mucosal and submucosal tissue in that spot.

Thus instead of blaming the stomach we should perhaps seek the basic abnormality of function leading to duodenal ulcer in the duodenum itself. Ordinarily the neutralizing capacity of the secretions entering the duodenum, primarily bile and pancreatic juice, is sufficient to protect the duodenum against the insult of gastric juice. In that case perhaps in some patients the reflux backwards into the duodenal bulb is not sufficient to supply the necessary neutralization at that level. Do Brunner's glands in the bulb area secrete a protective substance which becomes inadequate in some instances to prevent damage?

Then, of course, there is the known fact that the duodenum is normally the site of origin of inhibitory influences on gastric function. Acid in the duodenum activates certain reflex pathways that inhibit gastric function, and motor and secretory activity, and that releases from the mucosa a humoral agent or agents that have the same effects. This is why some have suggested that duodenal ulcer results from a failure of these inhibitory mechanisms, thus exposing the duodenal mucosa to a more prolonged and more concentrated assault from the stomach.

Then, of course, it may not always be the stomach nor the duodenum but the pancreas which is the source of the trouble. Here discrete tumors originating from islet tissue can release a secretory hormone that causes the stomach to pour out acid in amounts too large for the duodenum to withstand. There may even be no actual tumor formation but rather overactivity of these islet cells that produce the same substance.

Besides endogenous factors in the pathogenesis of duodenal ulcer we also must consider the pos-

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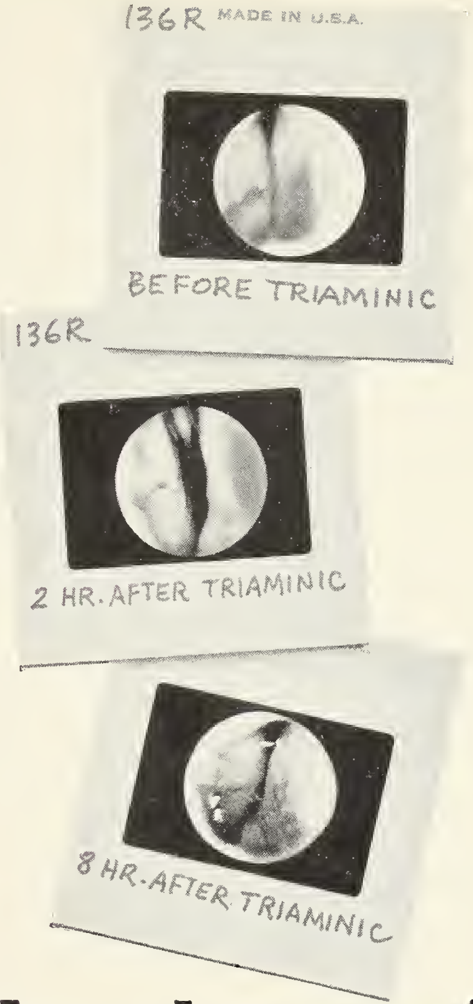

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sible role of exogenous factors. The regimen prescribed by many physicians to bring about healing and to prevent recurrence of the ulceration, requires complete abstinence indefinitely from all roughage and spices as if mechanical or physical or biochemical properties of certain foods serve to initiate or elicit the corrosion of the duodenum. Thus far, however, there has been no proof for this view namely that a certain diet is a salvation of a kind for the duodenal ulcer patient. However, unless we have something to blame the patient for, we are often put in a difficult therapeutic situation unless we prescribe diets and other restrictions to duodenal ulcer patients. There are certainly enough patients who are refractory anyway whatever we do.

There are many other factors in addition to endogenous and exogenous ones. There are recognized hereditory predispositions leading to duodenal ulcer as witness the high incidence of this disease in members of a single family. Investigations in this area might uncover a common denominator in the pathologic physiology in these people.

Then there are the well documented observations that ulcers heal during pregnancy and exacerbate during lactation. Also it is recognized that the control of duodenal ulcer may become very difficult after the menopause. Clearly the role of the female hormones on an ulcer require a great deal more research as regards their effects on the upper gastrointestinal tract.

With all these factors recognized as related to ulcer formation it is obvious we cannot speak of the pathogenesis of duodenal ulcer as though there is only one disturbance to explain all duodenal ulcers in all patients. There may be many aberrations in physiological mechanisms acid secretion and neutralizing mucin production, lack of epithelial resistance to ulceration and a variety of mechanical factors and neuro-humoral derangements. All have been implicated in causation and development of the lesion.

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THE INDICATIONS FOR MEDIASTINOSCOPY

Joseph P. Dineen, M.D.

■ The cervical approach to the mediastinum has been known since the initial operations of Heidenhain,[15] and Rasumowski[24] in 1899, and von Hacker[13] in 1901. The approach was then used primarily for the treatment of mediastinitis, but was also used by Marschik[19] for the prevention of mediastinal infection after war wounds. The first attempt to obtain mediastinal lymph nodes for diagnosis was made by Daniels[8] in 1949. His classic description of prescalene node biopsy was carried further by Harken[14] in his dissection of the mediastinum through the scalene biopsy incision, and in the visualization of the paratracheal lymph nodes with the laryngoscope.

The currently used method of mediastinal exploration was introduced by Carlens[4] in 1959, with an anterior midline approach through the suprasternal notch area. Since that time, extensive experience has been obtained in a number of medical centers, but the major credit for the development of this technique belongs to the Scandinavians. During the past twelve months, mediastinoscopy according to the method of Carlens has been introduced as a routine diagnostic procedure at the Veterans Administration Hospital in West Haven. In this first year, 21 examinations have been performed and a protocol established for the use of this modality.

Technique

The patient who is to undergo mediastinoscopy is prepared in the usual manner as for general anaesthesia. Following endotracheal intubation, a 5 centimeter long transverse incision is made 2 centimeters above the suprasternal notch, and subplatysmal flaps are developed. The strap muscles are separated in the midline and the pretracheal fascia incised. By means of blunt dissection the index finger is carefully inserted along the anterior wall of the trachea as far as possible. Usually this will enable the operator to palpate the right and left tracheo-bronchial angles, but the digit will not ordinarily reach the subcarinal area. An evaluation is made of any palpable evidence of invasion or fixation of the mediastinum. Any enlarged nodes or other abnormality in the paratracheal areas are noted. The 16.5 centimeter Carlens mediastinoscope (Fig. I) is then inserted and further dissection carried out. The right pulmonary artery crossing anteriorly below the carina is identified and the azygos vein likewise cleaned sufficiently for recognition. With the dissector or the suction tip, the subcarinal nodes are loosened as well as the paratracheal nodes. Biopsies are then taken of any suspicious nodes. In addition routine biopsy samples are obtained from six predesignated areas. Gelfoam pledgelets are applied to the biopsy sites if necessary, and the platysma and skin approximated in layers with 4-0 silk sutures. No topical antibiotic or drain is used. A scalene node biopsy, if not previously done, may then be performed under the same anaesthesia. Two illustrative cases are briefly presented.

Case Presentations

Case. 1. WHVAH 040-07-30-99 W. H., a 53 year old white male lithographer was admitted with a six day history of hoarseness and blood streaked sputum. He had been a moderately heavy smoker and noted a chronic productive morning cough for the past 20 years. X-rays revealed a mass lesion with central cavitation in the posterior segment of the right upper lobe. The PPD was positive in intermediate strength. Sputum cytologies and smears for AFB were negative on multiple occasions. Laryngoscopy, bronchoscopy, and scalene node biopsy were negative. At mediastinoscopy there was no gross evidence of metastatic disease or unresectability. Multiple routine biopsies were obtained. Initial examination of the pathology slides revealed only hyperplastic anthracotic lymph nodes. Step sections of the submitted material were then made and tumor was found in one sinusoid of a node taken from the right paratracheal area above the azygos node group. Mucin stains were negative and the tumor identified as a moderately differentiated epidermoid carcinoma. The patient is receiving supervoltage radiation to his tumor and to the mediastinum. He will be reevaluated for thoracotomy following this.

Case 2. WHVAH 042-07-54-00 L. C., a 59 year old white male school bus driver was admitted with a two month history of cough which was productive of small amounts of sputum and associated with band like pleuritic chest pain.

From the Surgical Service, Veterans Administration Hospital, West Haven, Connecticut, and the Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

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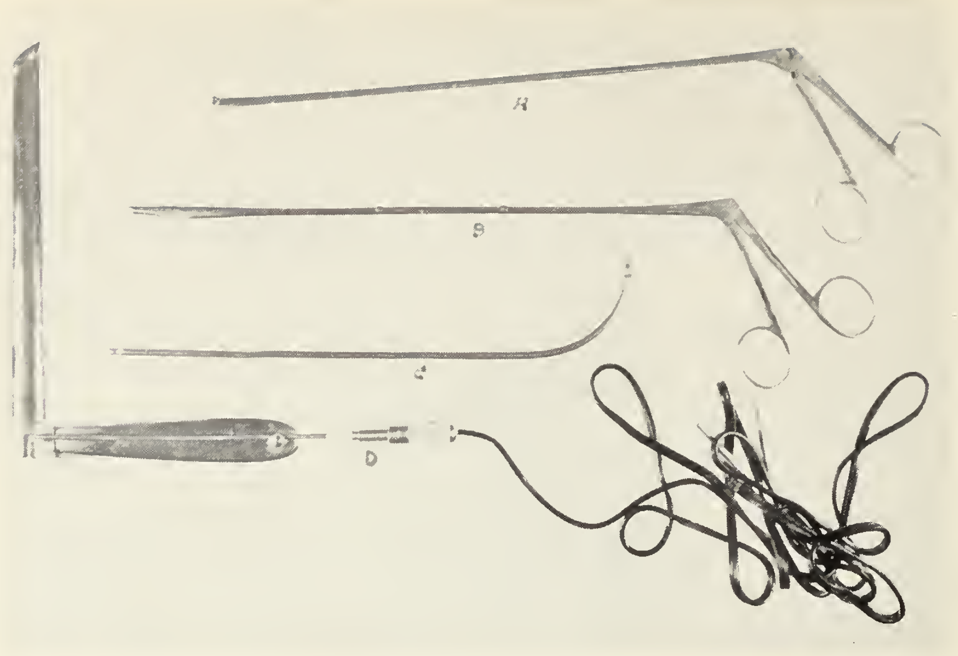

FIGURE 1
Demonstrated are: A. cup shaped biopsy forceps; B. alligator forceps used with gelfoam or cottonoid pledgelets as dissector; C. long suction tip, also used for dissection; and D. Carlens mediastinoscope, 16.5 centimeters.

Roentgenograms revealed a cavitating mass lesion in the posterior basal segment of the right lower lobe and evidence of partial atelectasis on the left. Bronchoscopy demonstrated narrowing of the left main stem bronchus two centimeters distal to the carina, with a firm white-yellow lesion on the posterior and lateral walls. Biopsies disclosed an epidermoid carcinoma. Multiple biopsies of a suspicious area in the posterior basal segmental bronchus on the right were negative for tumor on two separate bronchoscopies. The scalene node biopsy was negative. At mediastinoscopy there was no gross evidence of metastatic disease, invasion or fixation of the mediastinum. Routine biopsies were taken and metastatic epidermoid carcinoma found in the subcarinal nodes. The paratracheal nodes were negative for tumor. The patient is receiving radiation therapy.

Comment

In case 1, the positive biopsy of the paratracheal nodes represented the only positive diagnostic material obtained on this patient prior to the planned thoracotomy. The finding of positive material only after step sections had been made has been the experience of other investigators,[22] and all biopsies, if negative, now have serial sectioning. The second patient with proven carcinoma of the left main stem bronchus would most likely have received radiation therapy because of the probability that the contralateral lesion in the right lower lobe was also malignant, whether metastatic or a separate primary. The mediastinoscopy however documented the presence and extent of secondary mediastinal involvement prior to therapy. This should be of value in assessing the effects of radiation, and in planning any future surgical procedure.

Results

There was no mortality in the group of 21 patients. One of the patients demonstrated a fever ranging from 100 degrees to 102 degrees Fahrenheit post mediastinoscopy. During this time he had evidence on x-ray of cavitation developing in his right lower lobe tumor, and had considerable sputum production. With vigorous postural drainage and endotracheal suctioning his temperature returned to normal in four days. There was never any evidence of wound infection, mediastinal widening or pneumomediastinum. The remaining 20 patients were completely uncomplicated.

During the initial experience with the procedure, only two of the first nine patients had biopsies taken. Both of these were returned chronic lymphadenitis. In the last twelve cases, all patients have had biopsies taken routinely. The tissue diagnoses obtained in the entire group were:

Metastatic carcinoma from lung	2
Tuberculous granuloma	1
Silicosis	1
Non-caseating granulomata, hyperplasia & fibrosis	1
Hyperplastic anthracotic nodes	3
Chronic lymphadenitis	3
Normal nodes	3

To this time, seven patients with negative mediastinoscopies have been explored. Five of these patients have been resected. Two patients were found unresectable. The first of these was non-resectable because of extension into the posterior aspect of the aortic arch. The tumor lay outside the field of the mediastinoscopy. However, this was the first patient in the series, and he had already undergone protocol preoperative radiation. There was some adherence of the mediastinal tissues to the anterior wall of the trachea, and because of these factors, the examination was not as thorough as that now performed. Also, in general the procedure is avoided in radiated patients, and is now performed routinely prior to radiation to the mediastinum.

Discussion

The primary value of mediastinoscopy revolves about the problems posed in the management of patients with carcinoma of the lung. Lung cancer continues to increase in incidence, with 55,000 new cases a year and an annual mortality rate of 50,000 in the United States.[3] It is the most common visceral cancer in the male. Resectional surgery and supervoltage radiation have reached advanced states of development without significantly altering the generally dismal survival figures. The main hope of defeating cancer of the lung, namely prevention, will never be practical until it can be achieved without interfering with the inclinations of free human nature. For the present however, improvement can be made by refining our knowledge of the course and spread of the disease in the living patient, and by clarifying the role of surgery, radiation and chemotherapy in its management based on this knowledge.

It has been demonstrated by Delarue[9] that elimination of the exploratory thoracotomy to determine non-resectability will in itself probably double the 5-year survival figures. This is due to two major considerations. Firstly, the "fruitless" thoracotomy carries an average mortality of 10 per cent, with as high a rate as 16 per cent[21] reported, not to mention a complication or morbidity rate of up to 55 per cent as reported by Reynders.[25] Secondly, of all thoracotomies performed for patients with carcinoma of the lung, an average of 40 per cent disclose a non-resectable tumor. Larsen and Cliffton[16] record a non-resectability rate of 54 per cent of all thoracotomies for carcinoma at the Memorial Hospital in New York. The cause of non-resectability in 86 per cent of the cases of lung carcinoma studied by Reynders[25] is the secondary involvement of the mediastinum.

The presence of mediastinal involvement in general is considered to indicate at least incurability, and often non-resectability. What effect supervoltage preoperative radiotherapy will have in this group of patients remains to be determined. There is disagreement as to the role of extended resections, and palliative resections. The European experience indicates that these procedures in the face of mediastinal involvement, in addition to carrying a significant mortality, are also fraught with a high rate of complications, usually worsen the patient's disease process, and shorten his life expectancy.[2] In contrast to this, a number of American investigators[12,26] have been encouraged in the performance of supra-radical operations, and Strug[26] has reported that 50 per cent of the 5-year survivors at the Charity Hospital in New Orleans had mediastinal involvement at the time of resection. It can thus be reasonably stated that much more basic information needs to be obtained referable to the location and extent of mediastinal pathology and its correlation with the various therapeutic modalities. All other factors being equal, the key to a more rewarding approach to the treatment of lung cancer, and to the improvement in the salvage rates, lies in a thorough and systematic assessment of the state of the mediastinum prior to treatment.

The prescalene node biopsy while representing an advance in our approach to the mediastinum, and of definite value, has proven to have serious drawbacks. The nodes removed are at a distance from the primary pathology, and when involved usually indicate a far advanced situation with little hope of securing lasting benefit from any of the modes of treatment. It has been shown that where the prescalene node biopsy is performed in patients without palpable adenopathy in the area, the yield of positive material averages 7 per cent. In addition, in a large collected series[25] of 223 negative scalene node biopsies, 47.5 per cent of these patients were found to be non-resectable at thoracotomy.

In contrast to this are the results of mediastinoscopy performed on patients who otherwise have no contraindication to thoracotomy and resection, as a last step prior to surgery. In these patients who have no demonstrable evidence of mediastinal involvement by all the conventional diagnostic tests, Pearson[23] has found a positive mediastinoscopic biopsy in 33 per cent. Other large series vary between the 30 per cent positive rate of Bergh[1] to the 37 per cent rate reported by Reynders.[25] As expected, the biopsy is more likely to be positive with central or hilar lesions, but positive results have also been obtained with peripheral primary lesions in from 10 per cent of cases to the 26 per cent reported by Maassen.[18] Of importance also is the finding of positive tissue on the contralateral side in 20 per cent of the positive cases, a finding which would not be discovered at thoracotomy.[25]

Of perhaps greater significance has been the marked improvement in resectability rates since the introduction of mediastinoscopy. The resectability rate of Boerema[2] in Amsterdam, once 60 per cent, has been raised to 91 per cent in those patients who have a negative mediastinoscopy. Van der Schaar[27] has now reported a resectability rate of 93 per cent. The same author reports that in those patients who have been explored despite a positive mediastinoscopic examination, there is a non-resectability rate of 77 per cent. Around the world, over 1,000 mediastinoscopies have now been performed[6] and the results in all series consistently support these figures.

In addition to its great usefulness in assessing operability, mediastinoscopy has also been of striking value in providing a tissue diagnosis not obtainable by any other means. In carcinoma of the lung, approximately 40 per cent of the patients who have completed their evaluation, will have their only positive diagnostic material provided by mediastinoscopy.[20] Bergh[1] has reported that his incidence of positive preoperative diagnosis with the use of mediastinoscopy has been improved from 32 per cent to 52 per cent.

In sarcoidosis, Löfgren[17] has found the scalene node biopsy to provide diagnostic material in 32 per cent of the patients when there were no palpable neck nodes as compared to a 91 per cent positive rate with mediastinoscopy in the same type patient. Carlens[5] reports a 96 per cent positive mediastinoscopic biopsy for sarcoid in patients suspected of the disease without other proof of diagnosis.

Efskind[10] has found the examination useful in patients with carcinoma of the esophagus, and has obtained positive mediastinal nodes where the primary lesion has been in the lower third of the esophagus. The procedure has provided diagnostic material in silicosis, tuberculosis, and lymphoma. At present in this center studies are in progress to determine its usefulness in the diagnosis and staging of patients with Hodgkins disease or other malignant lymphomata.

Carlens[6] has reported its value in cases of severe hypertrophic pulmonary osteoarthropathy where the primary lesion is on the right. It is possible to section the right vagus nerve below its recurrent laryngeal division through the mediastinoscope, and significant improvement in symptoms has been noted following this technique. Carlens[7] has also recently reported the use of mediastinoscopy to implant the atrial-triggered pacemaker in patients with intermittent complete heart block.

Complications

The operative mortality of mediastinoscopy in reviewing a number of the largest series,[1,6,12,20,25,27] totalling 1500 cases was 0.3 per cent. Of the five deaths reported, two were definitely not related to the procedure. The most serious complication is hemorrhage which has occurred in less than 1 per cent of cases and has usually been due to inadvertent biopsy of the azygos vein or superior vena cava.[20] One laceration of the aortic arch[25] and one of the right pulmonary artery[22] have been reported. Thoracotomy has in several instances been necessary to control bleeding. Pneumothorax occasionally occurs but is generally no problem, only rarely requiring intubation. Injury to the left recurrent laryngeal nerve has been noted several times[25] but as a rule the nerve regains its function within several weeks. Reynders[25] and Farrow[11] have each reported one instance of tumor implant in the cervical wound. Infection, namely mediastinitis, has not been reported, and wound infection has been exceedingly rare. Local antibiotics have been used by some writers and not by others. In the early West Haven series, systemic antibiotics have been used for five days, but their necessity is certainly open to question. The overall incidence of complications has been extremely low and in general these have occurred early in each author's series. These figures compare quite favorably with the 10 per cent mortality and high complication rate attending the "fruitless" thoracotomy.

Contraindications

No patient is studied with this technique if there are any medical contraindications to a general anaesthesia or evidence of metastatic tumor outside the thoracic cavity. The patient must also be either a candidate for thoracotomy or manifest sufficient pulmonary reserve to permit a potential thoracotomy. The examination is not performed if there is infection in the area of operation, furuncles, a fistula or tracheostomy. It would be extremely difficult and hazardous in the face of superior vena caval obstruction. In addition, if the trachea is deviated and fixed behind one or the other of the sternoclavicular joints, it is not possible to introduce the mediastinoscope, as this writer discovered on one of the cases early in this study.

A word of caution! The examination is not lightly undertaken. A period of extensive anatomical review and cadaver dissection with the mediastinoscope is necessary prior to initiating the study in the clinical setting. The view of the anatomy is quite different from that observed at thoracotomy. The best results are obtained where the examination is performed routinely by one physician who has developed an experience and who has an interest in this method, whether he be otolaryngologist or thoracic surgeon. The support of an interested pathologist must be enlisted to aid in the study of the material obtained, which at times requires multiple sectioning.

The patients tolerate the procedure quite well and the postoperative discomfort is minimal, being generally less than that following bronchoscopy. The procedure while requiring somewhat longer initially, can with experience be accomplished in 20 to 35 minutes depending on the ease of dissection. It is most often performed under general endotracheal anaesthesia for better relaxation and for surer control of any incidental pneumothorax. It may be accomplished under local anaesthesia and Ward, et al.[28] have recently reported 25 cases with this technique and prefer it to general anaesthesia.

Summary

The experience obtained with 21 mediastinoscopies during the period April 1, 1966 to April 1, 1967 at the West Haven Veterans Administration Hospital is meagre compared to that compiled by Carlens,[6] Palva,[22] and others. However, it is a beginning. While the initial results have little statistical validity, the practicality and safety of the procedure have been demonstrated. At the present time, all patients with proven or suspected carcinoma of the lung have multiple biopsies taken not only from suspicious nodes, but from six predesignated areas; namely: 1. subcarinal, 2. azygos node area, 3. right mid paratracheal, 4. left tracheobronchial angle, 5. left mid paratracheal, and 6. mid pretracheal.

The presence of mediastinal involvement is staged according to site and extent, gross or microscopic involvement, involvement of more than one nodal area, fixation of the mediastinum, or gross invasion. Patients with positive biopsies receive supervoltage radiotherapy and are then reevaluated for thoracotomy. Patients with otherwise negative evaluations plus a negative mediastinoscopy are operated on.

Five years ago, mediastinoscopy was undergoing development in a few medical centers and its use was generally regarded with caution. It is probable that five years from now, all thoracic surgeons will insist on, and be able to obtain the information provided by this procedure prior to instituting treatment.

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KNOWLEDGE AND IGNORANCE, PRIDE AND POWER

Absolute knowledge could, therefore, leave nothing outside itself; and only on condition of knowing everything could man be granted its attainment. Man behaves as if he were destined to reach this absolute knowledge; and the incessant *why* which he puts to nature proves it. Indeed, this hope, constantly disappointed, constantly reborn, sustains and always will sustain successive generations in the passionate search for truth.

Our feelings lead us at first to believe that absolute truth must lie within our realm; but study takes from us, little by little, these chimerical conceits. Science has just the privilege of teaching us what we do not know, by replacing feeling with reason and experience and clearly showing us the present boundaries of our knowledge. But by a marvellous compensation, science, in humbling our pride, proportionately increases our power. Men of science who carry experimental analysis to the point of relatively determining a phenomenon doubtless see clearly their own ignorance of the phenomenon in its primary cause; but they have become its master; the instrument at work is unknown, but they can use it. This is true of all experimental sciences in which we can reach only relative or partial truths and know phenomena only in their necessary conditions. But this knowledge is enough to broaden our power over nature. Though we do not know the essence of phenomena, we can produce or prevent their appearance, because we can regulate their psysico-chemico conditions. We do not know the essence of fire, of electricity, of light, and still we regulate their phenomena to our own advantage. We know absolutely nothing of the essence even of life; but we shall nevertheless regulate vital phenomena as soon as we know enough of their necessary conditions. Only in living bodies these conditions are much more complex and more difficult to grasp than in inorganic bodies; that is the whole difference.—Claude Bernard, M.D. *An Introduction to the Study of Experimental Medicine*. New York, The Macmillan Company, 1927, p. 82.

GASTRIC SYPHILIS:

A Case With Pernicious Anemia

H. David Frank, M.D., Milton M. Lieberthal, M.D., and Russell H. Pope, M.D.

■ Clinically recognizable involvement of the stomach by syphilis is not a rare occurrence. Apparently this is true of all stages of the "great imitator." Moreover, the criteria for the diagnosis of gastric syphilis have been quite well established. The purpose of this report is to present a case of tertiary syphilitic gastric involvement simulating scirrhous carcinoma but with the unusual feature of a complicating pernicious anemia, hitherto unreported. The hematologic, secretory, radiologic, gastroscopic and histologic studies of this patient will be presented in detail.

Case Presentation

A 44-year old colored married female kitchen helper was admitted to the Bridgeport Hospital on March 2, 1965 complaining of weakness, shortness of breath, and swelling of the ankles. Aside from recent mental confusion, she had been in good health until December 1964, when she first noted easy fatigueability, swelling of the ankles, and progressively increasing shortness of breath. During the six weeks prior to admission she had been unable to work and had lost ten pounds in weight.

Her past history revealed no prior knowledge of lues or treatment for it. She had suffered the usual childhood diseases. She used no alcohol or tobacco, had never been pregnant, and her menses had ceased uneventfully at age 39. Her father had died of heart failure and her mother was living and well. She denied genitourinary symptoms. Her bowel function had been good and she denied anorexia.

Physical examination revealed her to be a thin, emaciated, confused Negro female, with pallor of her mucous membranes and severe exertional dyspnea. Her weight was 80¼ pounds, temperature 99°F, pulse 126, respirations 24, and blood pressure 130/60. Her tongue was swollen, beefy-red and smooth, and there was cheilitis. There was a regular sinus tachycardia and a systolic murmur was heard at the mitral area. The abdomen was distended and there was a questionable fluid wave. The liver edge was palpable 5 centimeters below the right costal margin. There was 4+ pretibial and 3+ sacral edema. Neurological examination was within normal limits, as were all other physical findings.

The admission blood count revealed a hemoglobin of 2.4 g/100 ml, a hematocrit of 10 per cent and a red blood cell count of 1,250,000/mm^3. Her MCV was 125 cubic microns, MCH 31 micromicrograms, and MCHC was 24 g/100 ml. The reticulocyte count was 0.1 per cent of erythrocytes. The white blood cell count was 3800/mm^3 with a normal differential. Bone marrow aspiration showed a megaloblastic hyperplasia. The prothrombin time was 38 per cent (18 seconds).

Gastric analysis with Histolog (2 mg/kg) yielded no free hydrochloric acid, with all specimens showing a pH between 5.8 and 7.0.

A Schilling test showed a 1.2 per cent absorption and a 12.5 per cent absorption when intrinsic factor was added (normal more than 8 per cent).

Serologic test for syphilis was positive in a dilution of 1:8 and the fluorescent treponemal antibody was reactive. The husband of the patient had a negative serology. Cerebrospinal fluid examination revealed the sugar to be 48 mg/100 ml, the protein 58 mg/100 ml, and no cells or growth on culture were found. There was a type II colloidal gold curve (23321).

Urinalysis showed a specific gravity of 1.016 with 2+ albumin and 30-40 white blood cells per high power field. Urine culture revealed the presence of paracolon bacillus. A 24-hour urine collection contained 4.7 g of protein in the 2375 ml volume.

The serum protein was 6.2 g/100 ml, albumin 3.2 g/100 ml. Serum electrophoresis demonstrated the following percentages: albumin 49.7 (normal 46.5-73%), alpha 1-globulin 1.6 (normal 1.7-6.5%), alpha 2-globulin 2.7 (normal 4.2-13.4%), beta-globulin 3.9 (normal 6.4-17.2%) and gamma-globulin 42.1 (normal 12.0-22.9%). The total serum bilirubin was 0.82 mg/100 ml (direct reacting 0.37 mg/100 ml, indirect reacting 0.45 mg/100 ml). Bromsulfalein retention was 9.4 per cent (a 5 mg/kg dose given and the specimen taken at 45 minutes). Lactic dehydrogenase was 1290 U, serum iron 32 μg/100 ml, and total iron-binding capacity 308 μg/100 ml.

The following studies were normal: fasting blood sugar, blood urea nitrogen, sodium, potassium, chloride, thymol turbidity, cephalin cholesterol flocculation, glutamic oxaloacetic transaminase, cholesterol and esters, amylase, calcium, phosphorus, protein bound iodine, T 3, test for sickling, lupus erythematosis cell preparation, hemoglobin electrophoresis, urine for Bence-Jones protein, urine urobilinogen, carotene, stool guaiacs, Coombs' test (direct and indirect), cold agglutinins, 4 stools for ova and parasites, stool fat, d-xylose absorption test, electrocardiogram, cervical Papanicolou, bronchoscopy, liver biopsy and liver scan.

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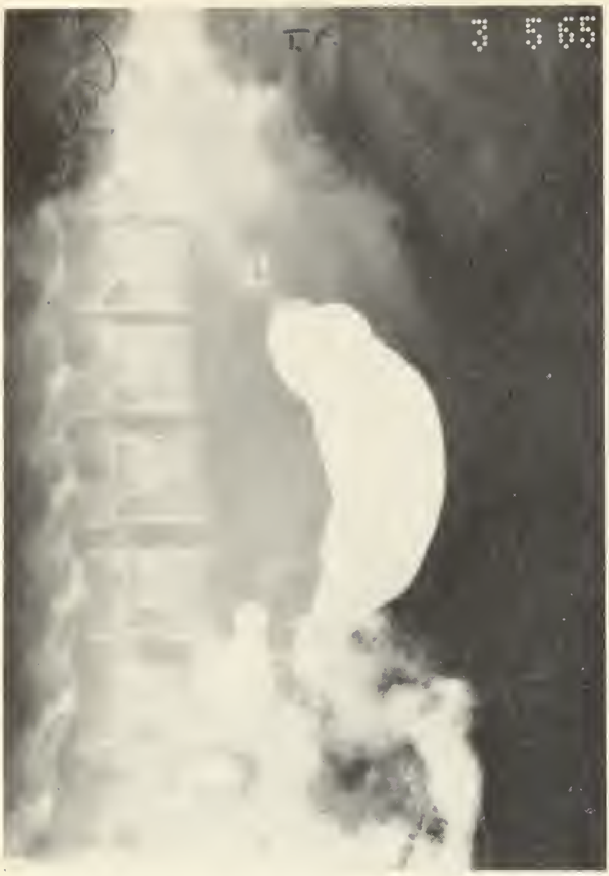

FIGURE I
Roentgenogram of the stomach on March 5, 1965.

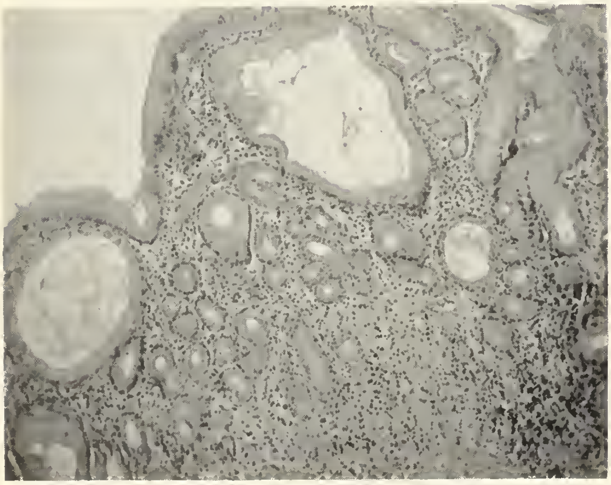

FIGURE II
This is the first gastric biopsy obtained March 9, 1965. There is intestinalization of the gastric glands with a few superficial glands dilated and filled with mucus. The lining cells vary from low to tall columnar and frequently contain mucous vacuoles. The interstitial tissue is abundant and infiltrated by chronic inflammatory cells, many of which are plasma cells. Hematoxylin and Eosin X100

The radiologic survey included a chest x-ray which revealed moderate cardiomegaly and a contracted left lower lobe with some pleural reaction. An upper gastrointestinal and small bowel series (fig. 1) showed tapering of the gastric fundus and a smooth wall of the body with abnormal stiffening. Peristalsis was present in the antral region only. These findings were interpreted as indicative of the presence of a linitis plastica. The barium enema and metastatic series were negative.

Gastroscopy with the Benedict Operating Gastroscope revealed distortion of the lower half of the stomach, making full visualization of the antrum impossible. The gastric walls appeared stiff and no peristalsis was seen. Mucosal folds were absent and the mucosa itself was a pale color. Several submucosal hemorrhages were visualized. A biopsy was taken (fig. 2). It contained many glands of varying sizes. The more superficial glands were dilated, containing scant mucus and were lined by tall columnar cells with frequent mucous vacuoles. The remaining glands were smaller with low columnar cells and less mucous secretion. The interglandular supporting tissues were heavily infiltrated by chronic inflammatory cells, many of which were plasma cells.

After the initial hematologic studies were completed, the patient received transfusions totalling 2000 ml of whole blood. She was also given 10 mg of vitamin K (Synkovite) daily by mouth. Her hemoglobin rose to 11.5 g/100 ml, hematocrit to 36 per cent, and red blood cell count to 3,800,000/mm^3. The prothrombin time reverted to normal. On March 15, 1965, daily vitamin B_{12} injections of 1000 micrograms were begun. However, the reticulocyte count over the next eight days never exceeded 1 per cent. On March 16, 1965, daily intramuscular injctions of B-complex vitamins and 600,000 units of procaine penicillin were begun. While the patient was receiving this treatment her confusion disappeared dramatically, the edema cleared, and she was discharged from the hospital on March 23, 1965 with a diagnosis of syphilitic linitis plastica, with secondary pernicious anemia.

The patient was re-admitted to the Bridgeport Hospital on May 31, 1965 for re-evalution. She was asymptomatic. Her weight was 108 pounds and physical examination was unremarkable except for cheilitis.

The hemoglobin was 14.1 g/100 ml, hematocrit 46 per cent and red blood cell count was 5,300,000/mm^3. Her MCV was now 87.5 cubic microns and the MCH 27 micromicrograms, MCHC 31 g/100 ml and the reticulocytes 1.4 per cent. The serum iron was 40 μg/100 ml.

The VDRL remained positive at 1:32, and the fluorescent treponemal antibody was still reactive.

The gastric analysis with Histolog (2 mg/kg) again revealed achlorhydria.

An upper gastrointestinal series was repeated (fig. 3), and this time showed improved distensibility of the fundus with normal peristalsis. However, mucosal folds were still absent.

Gastroscopy during this hospital admission permitted more complete visualization. The mucosa was still abnormal, however, and the stomach remained undistensible, with peristalsis not evident. Another biopsy was taken (fig. 4). This post-treatment gastric tissue showed a definite decrease in intestinalization and inflammation, although other changes noted in the first biopsy were still present. The interglandular supporting stroma was more abundant, loosely arranged and

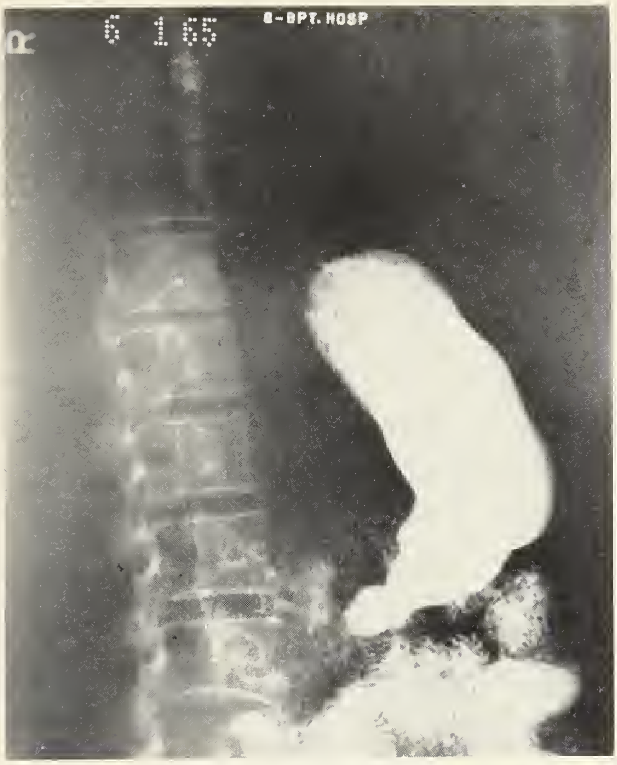

Figure III
Roentgenogram of the stomach on June 1, 1965.

edematous. Many cells were low columnar or cuboidal and mitoses were noted, indicating regeneration.

Penicillin was again administered (600,000 U daily for 15 days) after it was discovered that treatment had been inadvertantly terminated at the end of her first hospitalization, before the full course of antiluetic therapy had been com-

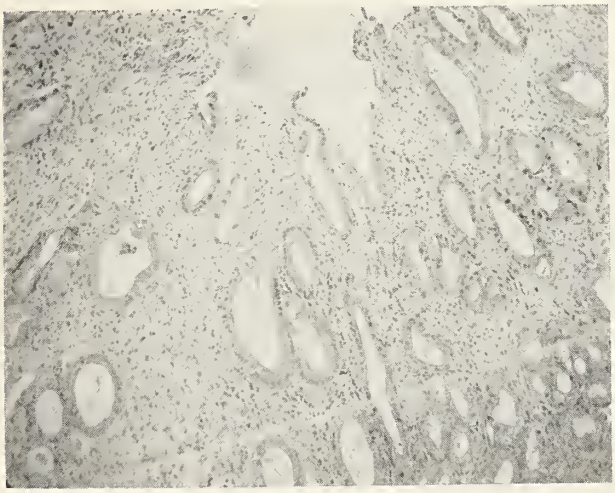

Figure IV
This is the second biopsy obtained June 4, 1965. Distortion of gastric glands remains but mucous secretion and vacuolization are not as prominent as in fig. 2. The interglandular fibrous tissue is very abundant and loosely arranged. The degree of inflammation is greatly decreased but a few plasma cells remain. Hematoxylin and Eosin X100

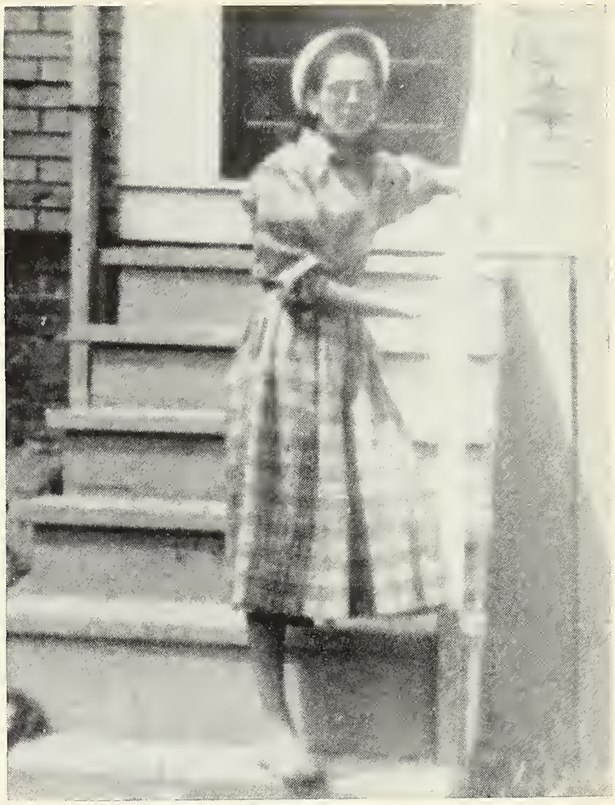

Figure V-a
Photograph taken prior to 1965, exact date unknown.

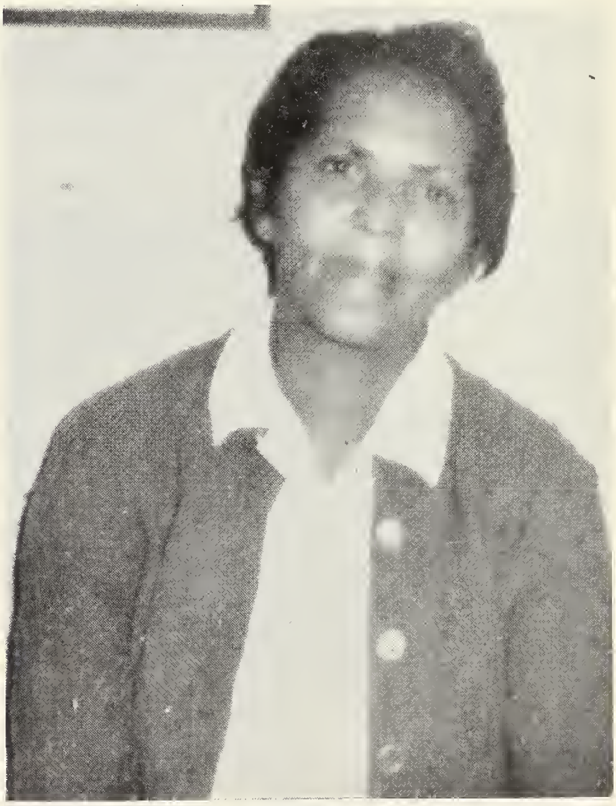

Figure V-b
Photograph taken in November, 1965.

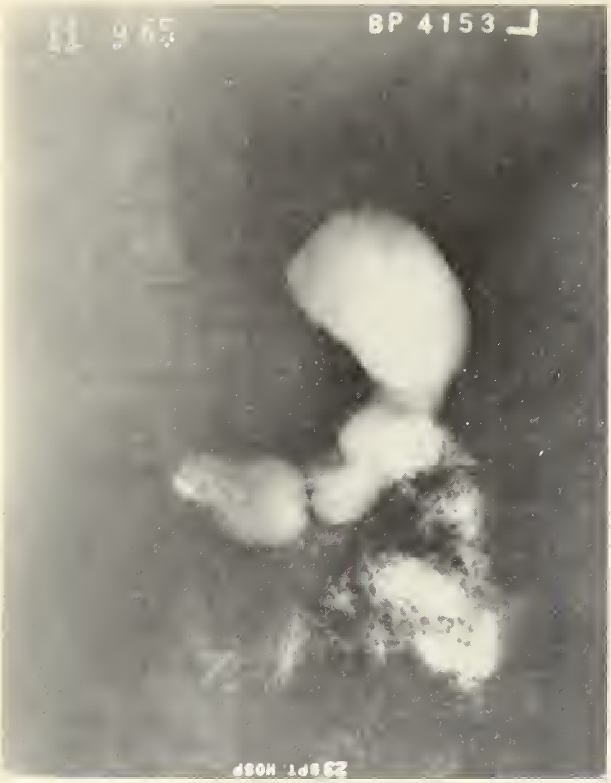

Figure VI
Roentgenogram of the stomach on November 9, 1965.

pleted. This time she was not discharged until she had received full treatment. She felt well.

Further studies were performed five months later in November 1965. She was still asymptomatic and weighed 125 pounds, making a total weight gain of 44¾ pounds. Her appearance had changed remarkably (fig. 5a and 5b). Cheilitis was still present, however. Tests for syphilis remained positive, titers unchanged. Complete blood count and cell indices remained normal. The serum iron was 27 μg/100 ml and no acid could be obtained from the stomach on maximal stimulation. The Schilling test was abnormal, as before.

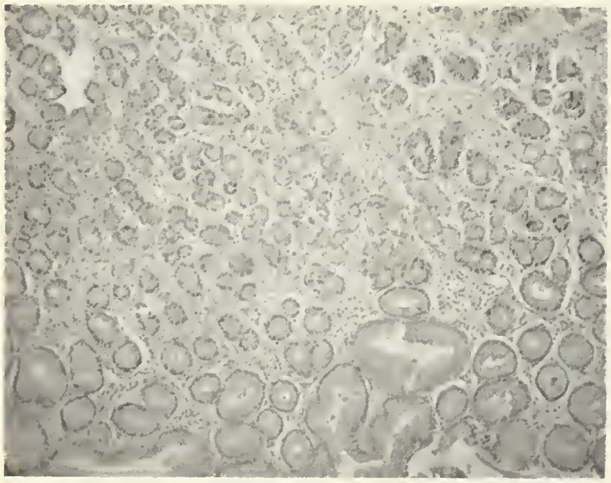

Figure VII
This is the third biopsy obtained November 9, 1965. The gastric glands are somewhat more numerous. Some of the lining cells still show some vacuolization. A few parietal cells are present. Interglandular fibrosis is less and inflammation is minimal. There is apparent partial regeneration of gastric glands. Hematoxylin and Eosin X100

X-rays of the stomach (fig. 6) showed a deformity similar to the one noted on previous admissions, though perhaps a little less marked.

Gastroscopy was again performed and a third biopsy taken (fig. 7). This biopsy, eight months after the first, showed the mucosa approaching normal. The glands had become more numerous and the entire thickness of the mucosa had increased. The lining columnar cells were of average height and many glands contained parietal cells not noted in the two previous biopsies. Mucous secretion was minimal. The amount of interstitial tissue and the number of inflammatory cells had decreased considerably.

As soon as the above follow-up studies had been completed, oral treatment with 0.3 g of ferrous sulfate t.i.d. was begun (on December 10, 1965), and by January 19, 1966 the serum iron had risen to 77 μg/100 ml.

The patient continued to feel perfectly well.

Discussion

The criteria for the diagnosis of gastric syphilis have become more definitive with our improved knowledge, technique and treatment.[1-3] Originally, pathologists refused to make this diagnosis because the spirochaetes could not be identified in the tissue involved. Moreover, in the few instances of suspected gastric syphilis in which spirochaetes were found, there is good reason now to suspect that they were merely saprophytes. However, if the pathologists' insistence upon bacteriologic confirmation had been persisted in, it would have made the diagnosis of tertiary syphilis in the cerebrospinal and cardiovascular systems a rarity, also. Moreover, with accumulation of cases, further study of their radiologic, laboratory and histologic features, and observation of the impressive results of specific antiluetic treatment—at first with heavy metals and in more recent decades with penicillin—there have now evolved diagnostic criteria for gastric syphilis which are reasonabley precise and quite dependable. These include: 1) the presence of untreated syphilis; 2) organic changes in the stomach seen by X-ray; 3) the lack of clinical or radiologic improvement with any other kind of treatment; and 4) the prompt occurrence of such improvement after specific treatment for syphilis.

The symptomatology of gastric syphilis may simulate any known organic stomach disease, or there may be no symptoms at all referable to the gastrointestinal tract, as in the case presented here. On the other hand, Stokes and Brown[4] analyzed 200 luetic patients whose chief complaint referred to the stomach, and found that 20 per cent actually had organic lesions of that organ. However, only 4 per cent of these were felt to be syphilitic in origin. When stomach involvement by syphilis does occur there is usually a gradual onset of mild postprandial discomfort, followed by early satiety, gradual weight loss, and, ultimately, starvation. However, long survival is possible even with maximal stomach involvement. In a Cabot case, Dr. Tracy Mallory[5] reported the 22 year survival of a patient with a stomach which was only 15 cm in length, with a lumen so small that it was hard to visualize fluoroscopically. The average age of the patient with gastric syphilis is usually 10-15 years younger than the average age of the group with gastric carcinoma, which most nearly resembles gastric syphilis clinically and radiographically. There is generally an absence of any signs of luetic involvement of other major systems.

The roentgenologic picture may vary considerably, and Bockus and Bank[6] have described 5 groups, according to the non-syphilitic pathologic lesion they most resemble. These include the group which imitate (1) gastric ulcer, (2) gastritis without achlorhydria, (3) diffuse fibrosis or scirrhous carcinoma, (4) gastric retention and (5) duodenal deformity. LeWald[7] felt, on the other hand, that the diagnostic criteria by X-ray were so characteristic that they actually made the diagnosis of syphilis. These criteria included the following five points: 1) diminished size of the stomach with rapid emptying; 2) a symmetrical deformity involving a large portion of the mid-body, without the cachexia that would be expected with a gastric carcinoma; 3) a linitis plastica type of deformity which may be difficult to differentiate from carcinoma, even in a young patient; 4) localized areas of infiltration similar to those seen with carcinoma, but more extensive and with a smoother outline than cancer shows; and 5) a stenotic lesion at the pylorus resembling cancer or ulcer, but which is always more extensive than the lesion in simple ulcer. Eusterman[2] and Moore[8] add to the above criteria the absence of a palpable mass despite the extensive radiologic involvement by a large and constant filling defect. It must always be remembered, however, that as frequent as the X-ray signs described above are in cases of gastric syphilis, they are much more frequently seen in gastric carcinoma. Sometimes, a return to a normal X-ray appearance may occur after treatment. However, permanent scarring may also be present, producing persistent roentgen defects, which is true of the case presented here.

As for the blood findings, numerous reports of other cases mention the occurrence of a mild to moderate anemia, but none record a macrocytic megaloblastic anemia as was present in our case. McPeak[9] reported a 62-year-old patient 6½ years after the onset of symptoms including great emaciation and a leather bottle type of stomach, whose hemoglobin was 46 per cent and red blood cell count 2,460/000mm.[3] In discussing the Cabot case[5] of the 22 year survival despite a severely attenuated stomach (referred to above) Dr. E. D. Churchill stated that "It is interesting that his blood is reported as being normal because we might look for the development of pernicious anemia." At the post mortem Dr. Mallory found an uninvolved antrum. Since this was at a time when the antrum was thought to be the site of origin of intrinsic factor, he postulated that the normal antrum explained the absence of pernicious anemia. We now know that the absence of intrinsic factor in pernicious anemia is due to involvement of the fundal mucosa.[10] But in spite of the total fundal involvement in the Cabot case, no pernicious anemia developed.

Studies of gastric secretion in cases of gastric syphilis have been reported by a number of authors. Eusterman[2] mentions achlorhydria or subacidity as one of his diagnostic observations. Williams and Kimmelstiel[11] found frequent achlorhydria, as did Spellberg[12] and Mitchell.[13] In some instances, the ability to secrete acid has been shown to return, while in others the achlorhydria persisted. This probably reflects an irreversible degree of damage to the mucosa. Bockus[14] describes a case in which there was a return of acid secretion by the stomach 3 years after (pre-penicillin) antiluetic treatment was started. By contrast, the return of acid secretory ability was described by Mitchell, et al,[13] to have occurred in as short a period as two weeks after penicillin treatment. One may wonder whether the more rapid treatment with penicillin will now more effectively and frequently reverse secretory abnormality than did the older slower treatments with arsenic, bismuth, mercury and iodides.

Gastroscopic observations have been made in a number of cases. Schwartz,[15] for instance, studied the gastric mucosal lesions of secondary syphilis, and found them to be similar to the mucosal lesions in the mouth and pharynx seen in this stage of the disease. He also found that these gastric mucosal lesions disappeared promptly after penicillin therapy. Palmer, Schindler, et al,[16] examined later stage syphilis and felt that they could not differentiate gastroscopically the lesion of tertiary syphilis from carcinoma, even retrospectively. This was true of our own experience also, although the biopsy findings of intestinalization and fibrous replacement without tumor cells, accompanied by plasma cell infiltration, were, at the very least, suggestive of syphilitic involvement.

However, the most striking feature in all cases of gastric syphilis is the clinical response to treatment in contrast to the frequent partial or complete failure of reversal of the laboratory, radiologic and gastroscopic abnormalities. This clinical response should be phenomenal, as indeed it was in this case. The patient's rapid weight gain above and beyond expectation was classic and diagnostic. Furthermore, within one week of the beginning of penicillin therapy, her edema and confusion disappeared, and she was clinically improved enough to warrant release from the hospital. Prior to this treatment her hematologic status was improved by blood transfusion, the hematocrit rising from 10 to 36 per cent. It is interesting that there was no reticulocytosis during the subsequent therapy with B_{12}. Some reticulocyte response might have been expected at this latter level. However, the presence of the concommitant iron deficiency may have prevented the formation of red blood cells in her bone marrow. And despite the fact that her final biopsy showed partial regeneration of the gastric mucosa, the Schilling test remained abnormal and the achlorhydria persisted. The radiological and gastroscopic improvement that occurred was not complete, and lagged far behind the clinical improvement.

Summary

A 44-year-old luetic female with pernicious anemia and the radiologic picture of linitis plastica is presented. Treatment with penicillin resulted in a complete clinical remission and partial histologic regeneration of the gastric mucosa. The gross deformities seen by X-ray and gastroscopy did not undergo remission, however, and persist to the present. An exposition of the diagnostic criteria is made, and the clinical, hematological, and radiographic features of gastric syphilis are discussed.

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THE CLASSIFICATION OF FETAL HEART RATE

II. A Revised Working Classification

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■ Organized and efficient analysis of fetal heart rate (FHR) and uterine contractions (UC) patterns recorded with continuous monitoring techniques depend to a large extent upon an adequate method of classification. Classification is also important as a means of communication between research and clinical groups especially since similar FHR changes have not been labeled uniformly by all investigative groups.[1-6]

Since the introduction of the instantaneous cardiotachometer for FHR studies[1] and the initial description of various FHR patterns[2] continuing experience has demonstrated the need for a broad FHR classification which makes provision for the details of individual FHR patterns. An earlier report[7] outlined a working classification of FHR which, in the main, has been satisfactory but is somewhat restricted since it relies heavily on descriptive terms. This report describes changes in the earlier FHR classification which make it less ambiguous and provides a more objective basis for computer analysis of FHR data.

Bases for FHR classification. Re-evaluation of many hours of FHR recordings led to the present concept. It is based upon the idea that a given FHR represents the output of a physiologic system which reflects the degree of control exercised by a number of opposing physiologic mechanisms which may have different time courses. In the antepartum period and between uterine contractions in the intrapartum period, the interplay of these mechanisms prescribes a unique FHR baseline level for each individual fetus. This level is held within fairly close limits as the result of the interaction of cardio-accelerator and cardio-decelerator reflexes, which are usually in relative balance, so that there is a continuous superimposed irregularity which reflects the continuous "hunting" (i.e., momentary oscillations about the FHR baseline as the opposing accelerator and decelerator reflexes attempt to achieve balance) of the control mechanism. If, for some reason, there is transitory imbalance between these two opposing control mechanisms it is reflected by a corresponding transitory FHR acceleration or deceleration.

While the present working FHR classification has been primarily designed for intrapartum studies, it is also useful for antepartum studies. However, the following discussion will be limited to the use of this classification in the intrapartum period. The following broad principles are used for classification:

1. FHR patterns are made up of two major segments (a) *baseline* changes, i.e., FHR alterations in the absence of, or in between UC (b) *periodic changes,* i.e., FHR alterations associated with UC. While these changes are not periodic in the strict sense of the word, they are quasi-periodic.

2. *Baseline FHR levels* are evaluated at 10 minute intervals and are described by designating an FHR range in which the baseline FHR is located during the major portion of a 10 minute interval. FHR accelerations or decelerations from the baseline, not associated with UC, short of 10 minutes duration are simply called "accelerations" or "decelerations." If the alteration in baseline is 10 minutes or more, this is considered a new FHR baseline.

3. *Periodic FHR changes* are classified primarily on the basis of waveform, and secondarily on the timing relationship between the beginning of a UC and the onset of an FHR change. Since periodic FHR changes are usually short-lived and closely related to UC, their transitory nature is implied, e.g., when the term "deceleration" is used, it describes a transitory fall in FHR from a given baseline level followed by a return to the baseline shortly there-

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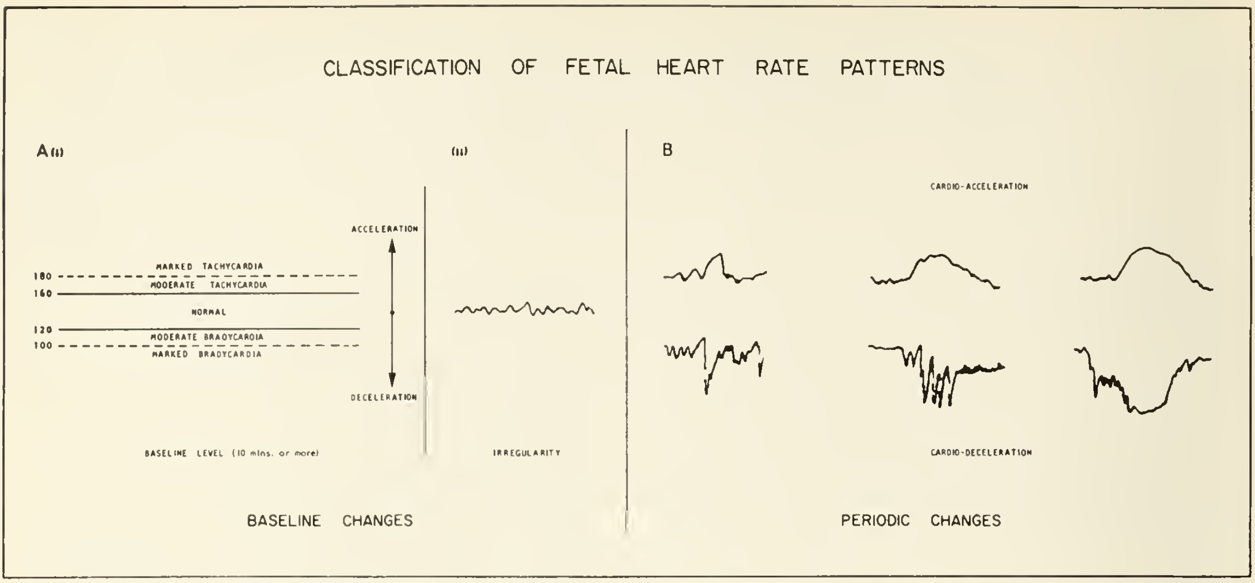

Figure IA (i)
Basis for labeling of FHR baseline level.

Figure IA (ii)
Example of FHR baseline irregularity.

Figure IB
Upper traces are examples of fetal cardiac acceleration of varying duration and amplitude. Lower traces, extmples of fetal cardiac deceleration of varying waveform, duration, and amplitude.

after. Descriptions of periodic FHR accelerations or decelerations are always preceded by an adjective describing their time relationship to a UC viz., "early," "late" or "variable." This labeling serves to distinguish them from accelerations or decelerations from the FHR baseline not associated with UC.

Illustrations

Overall Concept. Figure IA(i) illustrates the most widely used clinical FHR classification. The FHR between contractions is considered baseline and is evaluated every ten minutes. A new baseline is established if the baseline alterations last longer than ten minutes. Figure IA (ii) illustrates the baseline FHR irregularity which is present in varying degrees in almost all fetuses. This irregularity reflects the relative state of balance which exists between the cardio-accelerator and cardio-decelerator control mechanisms. The three upper traces of Figure IB are examples of transitory fetal cardiac acceleration which is frequently superimposed on the baseline FHR pattern. The three lower traces show similar transitory FHR decelerations. While these transitory imbalances of the physiologic FHR control mechanisms may be seen sometimes between contractions (i.e., in the baseline period) they are more commonly noted with uterine contractions.

FHR Acceleration. FHR accelerations from the FHR baseline between and with UC occur less frequently than FHR decelerations and hence have not been studied as extensively. However, in some instances a definite timing relationship exists between the onset of certain types of FHR acceleration and the beginning of a UC (See Figure IVD). The present revised FHR classification makes provision for separating baseline from periodic FHR accelerations in a similar manner at it does for FHR decelerations.

FHR Deceleration. The most frequent and prominent alterations in FHR patterns observed during labor are due to cardio-decelerator reflexes. The actual waveform of the periodic deceleration and the relationship of its onset to the beginning of its associated UC are useful in classification.

Figure II outlines a method of separating these periodic deceleration patterns into three specific categories. The first step is to look at the individual FHR waveform.* If the slope of the descending limb of the FHR pattern is falling faster than the ascending slope of the associated UC is rising, and if the FHR pattern *varies* in shape from contraction to contraction it is termed "variable deceleration"

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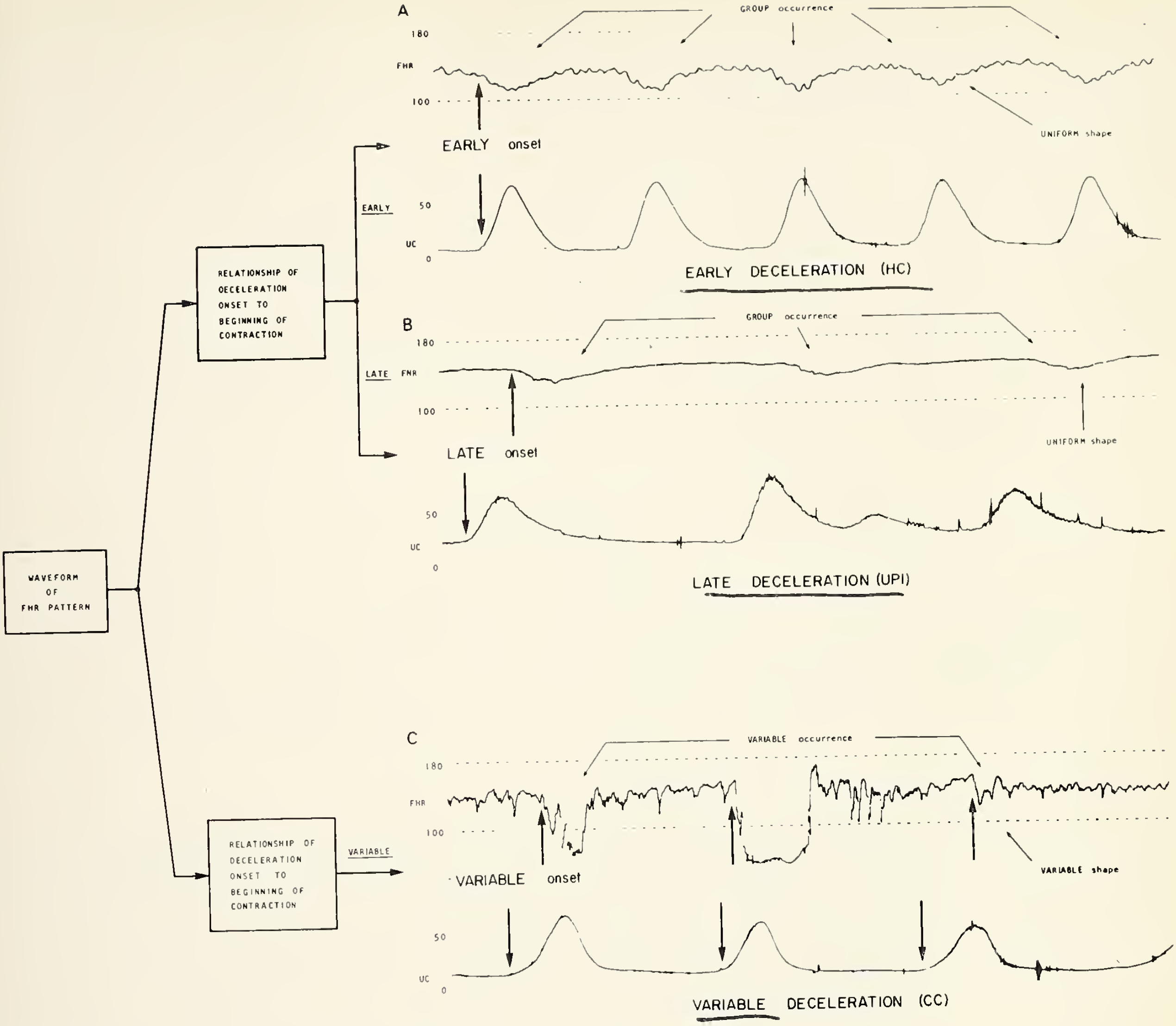
* The appearance of the FHR and UC waveforms are directly dependent on the vertical and horizontal scaling factors. This discussion is based on the following original trace scaling viz. a) FHR: 10 mm = 30 beats per minute, b) UC: 10 mm = 25 mms Hg. c) time base: 30 mm = 1 minute.



FETAL HEART RATE DECELERATION PATTERNS

FIGURES IIA, IIB, AND IIC

Flow diagram for classification of fetal cardiac deceleration. In Figure IIA, note the uniform shape of the FHR deceleration from contraction to contraction and its *early* onset in relationship to the beginning of the contraction. In Figure IIB, the FHR deceleration pattern is also uniform but has its onset *late* in the uterine contraction.

In Figure IIC, the FHR waveform *varies* markedly from contraction to contraction as does its onset in relationship to the beginning of the contraction.

(Figure IIC). If the FHR waveform is relatively uniform in appearance, and the slope of the descending limb is falling at about the same rate that the ascending slope of the associated UC is rising, so that each FHR pattern largely reflects the shape of the associated UC, the deceleration is further classified by considering the relationship between the onset of the deceleration to the beginning of the associated UC.

If the onset of the FHR deceleration coincides approximately with the beginning of the UC, so that it falls *early* in the contraction phase, it is called "early deceleration." The overall pattern of this type of deceleration is illustrated in Figure IIA. If the onset of the deceleration begins *late* in the uterine contraction phase, i.e., some 20 to 30 seconds or more after the beginning of the UC it is called "late deceleration." This overall pattern is illustrated in Figure IIB.

While this gross separation process enables identification of specific FHR patterns, it makes no provision for the degree of deceleration. Although

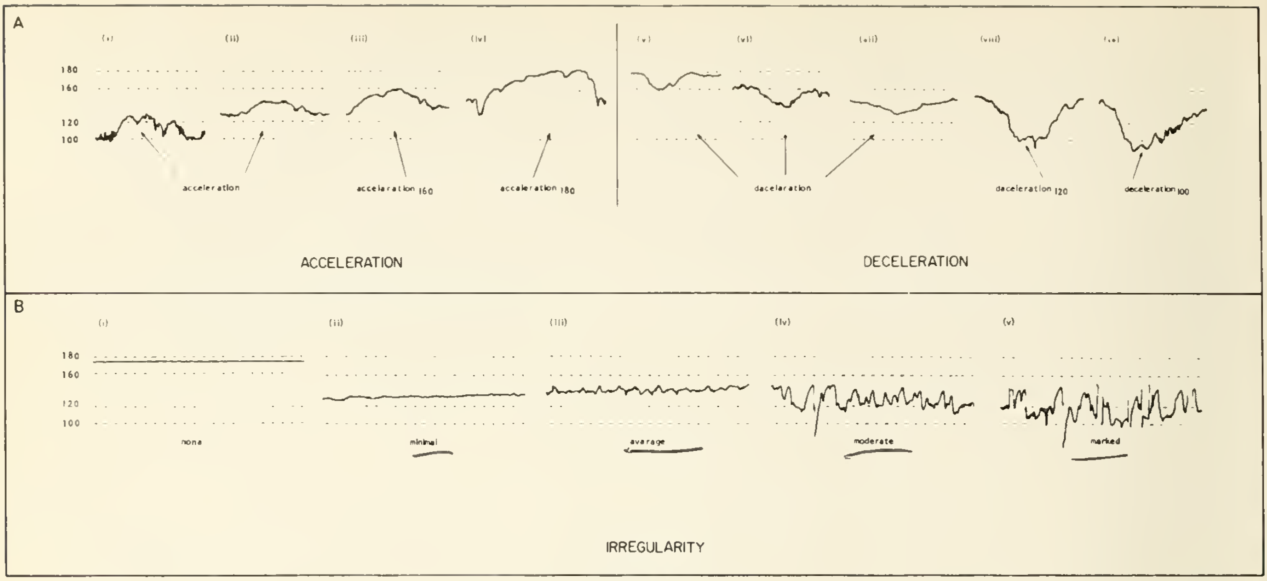


Figure IIIA (i-iv)

Examples of fetal cardiac acceleration. The subscript indicates the level which is reached, or exceeded by the maximum FHR. Where no subscripts are used, the maximum FHR does not reach the upper limits of the normal FHR range.

Figure IIIA (v-ix)

Examples of fetal cardiac deceleration. The subscripts refer to the level which is reached, or exceeded by the minimum FHR. In cases where no subscripts are used, the minimum FHR does not fall below the lower limits of the normal FHR range.

Figure IIIB (i-v)

Examples of varying degrees of FHR baseline irregularity.

the significance of a given level of FHR acceleration and deceleration is not understood at the present time, on the basis of past experience it seems reasonable to make provision for a certain degree of quantitation. Figure 3A illustrates a method which is based on the FHR limits used for classification of baseline FHR changes (Figure IA). FHR accelerations where the maximum does not exceed 160 beats per minute is simply designated "acceleration" (since it is an FHR change which is still in the normal FHR range). If the maximum FHR exceeds 160 beats per minute but is less than 180 beats per minute, it is designated "acceleration$_{160}$". Similarly if the maximum FHR exceeds 180 beats per minute it is designated "acceleration$_{180}$". Deceleration is treated in a similar manner, e.g., if the lowest FHR falls below 120 beats per minute this is termed "deceleration$_{120}$". Likewise, if the FHR falls below 100 beats per minute this is designated "deceleration$_{100}$".

FHR Irregularity. The amount of FHR baseline irregularity appears to be related somewhat to fetal maturity. It is modified to some degree by labor itself and can be markedly altered with autonomic drugs. Figure IIIB (i-v) illustrates some of the patterns encountered and the method used for rough quantitation. The numerical basis for classification is discussed later.

Figures IVA and IVD illustrate the use of this revised working FHR classification with examples of FHR patterns. Figure IVA is an example of a baseline FHR pattern of moderate tachycardia with minimal irregularity and periodic episodes of early deceleration of varying levels. While the FHR baseline is classified on the basis of the prevailing pattern for 10 minutes, each periodic FHR change is classified individually (in this case 2 of the 5 episodes have been labeled). Figure IVB illustrates a normal FHR baseline with average irregularity and periodic episodes of late deceleration. Figure IVC is an example of a normal FHR baseline with moderate irregularity and periodic episodes of variable deceleration. Figure IVD is an example of moderate tachycardia with average irregularity and periodic episodes of acceleration.

Definitions

The present working FHR classification is based on the following premises: a) a baseline FHR level for a given fetus b) a superimposed FHR irregu-

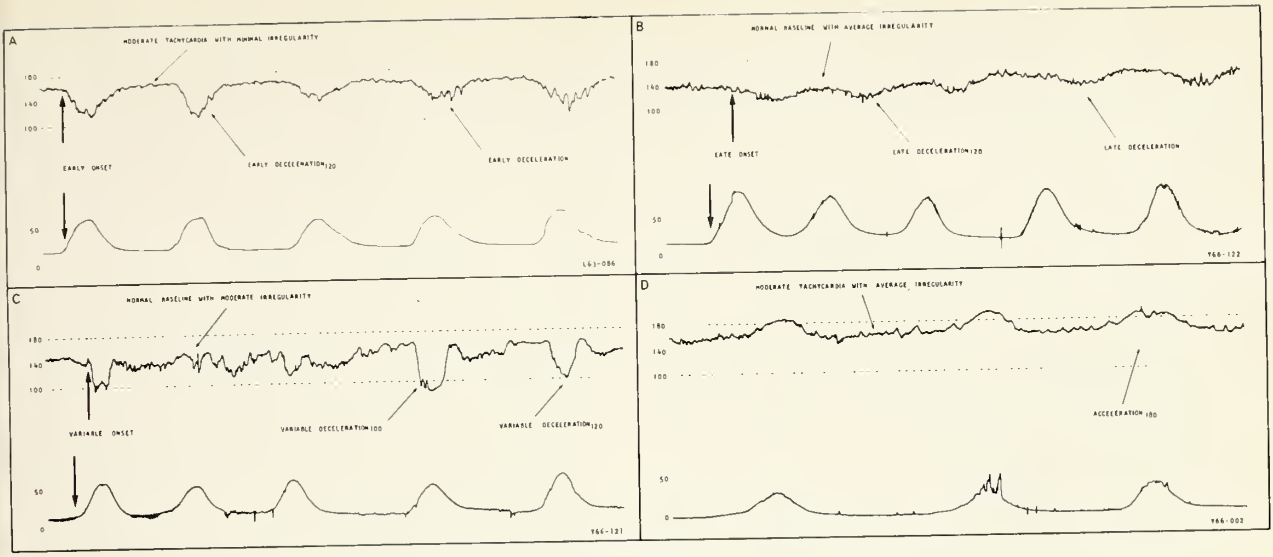


Figure IV A

Example of a baseline FHR which shows moderate tachycardia with minimal irregularity. The periodic FHR pattern is one of early deceleration.

Figure IV B

Baseline FHR showing normal FHR with average irregularity. The periodic FHR pattern is one of late deceleration.

Figure IV C

Baseline FHR of normal FHR with moderate irregularity and a periodic FHR pattern of variable deceleration.

Figure IV D

Baseline FHR pattern of moderate tachycardia with average irregularity and a periodic FHR pattern of acceleration.

larity of varying degree c) periodic alterations in baseline FHR associated with contractions and d) sporadic alterations in baseline FHR not associated with contractions.

Baseline FHR. The baseline FHR is evaluated over a 10 minute interval and is determined between uterine contractions or between FHR changes associated with uterine contractions, e.g., Figure IVB. If the patient is not in labor, only baseline FHR changes are described.

1. FHR level. The method of labeling FHR baseline levels used for the earlier working classification[7] has proved satisfactory and will be retained in this revision. They are as follows:

Normal	—120 to 160 beats per minute
Moderate tachycardia	—161 to 180 beats per minute
Marked tachycardia	—181 or more beats per min.
Moderate bradycardia	—100 to 119 beats per minute
Marked bradycardia	—99 or less beats per minute

"Normal," "bradycardia," and "tachycardia" are terms which are restricted to baseline FHR descriptions and are not used to label transitory manifestations of the cardio-accelerator and cardiodecelerator reflexes. This actual FHR baseline level is determined by the range into which the baseline falls for the majority of a 10 minute interval.

2. Irregularity, (Figure IIIB). Irregularities in the baseline FHR are classified on the basis of the amplitude of the FHR fluctuations which have a frequency of 3-5 cycles per minute. Amplitude is measured as a percentage of baseline level, viz.

(i) none—no visible fluctuations
(ii) minimal—less than 3 per cent of baseline FHR
(iii) average—4 to 9 per cent of baseline FHR
(iv) moderate—10 to 15 per cent of baseline FHR
(v) marked—greater than 15 per cent of baseline FHR

3. Sporadic FHR changes. Accelerations or decelerations in the baseline FHR which are not associated with uterine contractions are classified on the basis of:

a) duration: less than 30 seconds; more than 30 seconds but less than 2 minutes; more than 2 minutes but less than 10 minutes. If the change in FHR exceeds 10 minutes, this is considered a new FHR baseline.

b) amplitude: the method of classifying FHR amplitude changes is determined by the FHR level which is exceeded by the FHR acceleration or deceleration under consideration (Figure IIIA).

Periodic FHR Changes

1. Irregularity. Alterations in FHR baseline irregularity clearly associated with UC are classified in a similar manner to that used for baseline FHR changes without UC.

2. Acceleration. Periodic FHR acceleration associated with UC are classified similarly to those occurring in the FHR baseline (Figure IIIA (i) to (iv)).

3. Deceleration. FHR deceleration is classified on the following bases:

(a) Waveform and timing. As indicated in Figures IIA, IIB, and IIC, periodic FHR changes due to cardio-decelerator reflexes can be classified readily on the basis of waveform and timing into three specific categories, viz. "early," "late," and "variable." The "early" and "late" designations apply to FHR waveforms of uniform shape. Further separation is determined by the timing relationship between the onset of the deceleration and the beginning of the UC. In early deceleration the onset of the deceleration is almost coincident with the beginning of the UC. In late deceleration, the onset of the deceleration is delayed some 20 to 30 seconds after the beginning of the contraction. In the case of variable deceleration, each wave form has a variable shape which usually varies from contraction to contraction. This is also true of the timing of the onset of this type of deceleration and the beginning of the associated contraction.

(b) Duration. Less than 30 seconds; more than 30 seconds to less than 2 minutes; more than 2 minutes to less than 5 minutes; and greater than 5 minutes.

(c) Amplitude. Amplitude changes in periodic FHR accelerations and decelerations are labeled similarly to those for sporadic FHR changes (Figure IIIA (i) to (ix)).

Comments

In the clinical application of this method of FHR classification, it is not always possible to identify visually all FHR deceleration patterns, although with a little experience this can usually be done. Since it is possible for mixed FHR patterns to occur, there will be times where positive FHR pattern identification cannot be made. For this unusual situation, we use a classification entitled "deceleration, undetermined."

Analysis of thousands of hours of FHR recordings is a formidable task, and a technique, short of a detailed computer analysis of consecutive segments of individual FHR patterns must be provided. This revised working classification, in spite of its obvious shortcomings, when used with computer techniques for sorting and frequency counting has provided a more objective background for clinical evaluation of FHR than previously available. It also serves as a first-step editing process to direct attention to certain FHR patterns for detailed computer analysis, since at the present time it is not feasible to process entire labors even with a large digital computer. Only when specific FHR changes of clinical significance are delineated and clearly defined, will it then become feasible to process entire labors for these specific changes.

To mechanize the foregoing principles of FHR classification, flow diagrams, measuring scales, definition books and code sheets have been made. These techniques and the computer programs which have been written for handling the data will be reported later.

Summary

1. FHR patterns can be classified on the basis of *baseline FHR changes* which occur in the absence of, or in between uterine contractions and *periodic FHR changes* which are associated with uterine contractions.

2. Baseline FHR changes are evaluated at 10 minute intervals and are labeled by designating the range in which the baseline FHR is located.

3. Periodic FHR changes are classified on the basis of waveform and timing and are labeled for each individual uterine contraction.

4. While a working FHR classification of this type does not provide a detailed numerical analysis of FHR patterns, it is an important step towards an objective method for describing and analyzing FHR patterns.

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CRYOGENIC PROSTATECTOMY

A Preliminary Report

Vincent J. Longo, M.D.

■ It is the birthright of every human being to age gracefully. Too often, however, the status of senior citizenship carries with it the cumbersome burden of serious disease. Bladder outlet obstruction is a particularly loathsome infirmity which shortens life and makes the final years unattractive. Thirty years ago the mortality from prostatectomy was fifteen per cent; now it is about two per cent or less. But this still leaves too large a number of men who are denied emancipation from the catheter life because of the involved prohibitive surgical risk. This paper is a preliminary report on the management of thirteen such elderly poor-risk patients with advanced prostatism by cryogenic prostatectomy.

Through the years, many physical forces have been harnessed as surgical tools: sound, light, ultrasonic waves, heat, high-frequency heat, Laser systems, cold and profound cold. The application of chilling as a therapeutic modality was mentioned in the Edwin Smith surgical papyrus (3500 B.C.), and Homer wrote of something similar in the treatment of javelin wounds four thousand years ago. It was known during Napoleon's time that amputation of extremities was less painful among soldiers whose limbs had been overexposed to cold; in 1877 a Dr. J. V. Mott wrote a scientific paper on "medicated ice." Historically, the development of cryogenics (Gr. *kryos,* icy cold) was fostered by such workers as Bell, Arnott, Bennett, Cooke, Bright, Mitchell, Allen, Fay, Bigelow, DuBois, Hines and Merryman; in the past twenty years significant advances were made by Luyet and Gehenio, Rey, Smith and Parkes.[6] The recent engineering perfection of vacuum-insulated equipment plus the versatility of such men as Irving S. Cooper in neurosurgery and Doctors Soanes and Gonder in urology made possible the final breakthrough in clinical cryosurgery.

Thus, the application of refrigerants has been suggested in many fields—sometimes experimental, more or less successful, not always universally acceptable—as in neurosurgery (Parkinsonism and other movement disorders, deep-seated brain tumors, relief of intractable pain, Meniere's syndrome, hypophysectomy), urology (benign and malignant hyperprostate, bladder tumors), ophthalmology (cataract extraction, detached retina, intra-ocular tumors, glaucoma, storing frozen corneas), gynecology (cervicitis, conception control, abnormal uterine bleeding, malignancies), otorhinolaryngology (tonsillectomy, tumors of mouth and vocal cords), tumor surgery (skin, bone, liver, kidney, lung, rectum), burn therapy, dental diseases, preservation of whole blood, freezing of human and other animal sperm cells, biology (freezing and thawing of lower forms of life). So, it has recently been popularized that the *hottest* thing in science nowadays is cold![11]

What are the biologic effects of freezing? Following the phase of supercooling, ice crystals form at fifteen to twenty degrees below zero Centigrade; but all living tissue exposed to a temperature of −20°C. or lower for more than one minute will undergo necrosis. Liquid nitrogen, when subjected to a pressure of twenty-two to thirty pounds per square inch, achieves a temperature of −196° Centigrade (or −352.8° Fahrenheit); in this milieu of the coldest possible cold all molecular motion ceases. Because of its unique architecture, the prostate—within a tight capsule surrounded by a rich vascularity totally independent of the blood supply of the adjacent bladder, external sphincter and rectum—lends itself to total cryodestruction. Packed within this strong capsule, the prostate immediately expands 15 per cent in volume with freezing and this additional pressure results in early avascularization; natural thawing begins about fifteen minutes after termination of the freeze.

Living tissues exposed to this frigid domain are killed by one or more of these mechanisms: 1) dehydration and toxic concentration of electrolytes due to removal of water, 2) crystallization and rupture of cell membranes, 3) denaturization of liquid protein molecules within the cell structure,

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4) thermal shock leading to cellular death and 5) vascular stasis.

The pathologic effects of the cryodestructive process in the canine prostate gland have been well documented,[9] as follows:

Gross: 0-5 days: swelling, hemorrhage

12-22 days: prostate size diminished

Microscopic: 0-5 days: immediate necrosis; ghost cell formation; breakdown in cellular membranes; collection of nuclear detritus; marked tissue hemorrhage

9th day: fibroblastic activity at periphery; marked histiocytosis with hemosiderosis; ghost outlines of cells

14th day: necrosis; nuclear detritus; hemosiderin; beginning regrowth of immature tubules from periphery; advanced fibrosis; squamous metaplasia; minimal inflammation (unlike the usual vascular infarct!)

22nd day: maturation of glands; modest scar formation; minimal inflammatory reaction

28th to 45th day: regrowth of tissue with budding and branching.

The muscular walls of the larger arteries are extremely resistant to cold, even at the lowest temperatures, so that blood within these vessels will thaw and then continue to flow.

The reported biochemical effect of freezing is to suspend acid phosphatase enzyme activity in the prostatic tubular epithelial cells.

Equipment And Method

The Linde CE-4 cryosurgical unit* consists of a vacuum-insulated liquid nitrogen container and feed line, prostatic probe and assembly (similar to a size 26 Fr. urethral sound with a 2¼ inch long heat exchange chamber and built-in button guide) and control console with heater for regulating and recording temperatures. This recently perfected equipment enables the operator to freeze such a circumscribed area as the prostate gland into an ice ball. In the meantime, the liquid nitrogen is vaporized by the equilibrating transfer or withdrawal of heat from the tissue and the gaseous element escapes via the outer portion of the cannula. The size of the prostatic ice ball is determined by the probe freezing surface and temperature, duration of contact with tissue and heat transfer; the last is dependent on the rich blood supply and this acts as a built-in safety valve to forestall over-freezing.

Before the patient enters the operating room a preliminary mock test run is made to insure that all systems are A-OK and, most importantly, to prime the feed line. With the subject in lithotomy position under low saddle block or spinal anesthesia (tho it's possible to perform this operation with local topical anesthesia), direct-vision cystourethroscopic examination is effected; perineal needle biopsy may be done. The cryogenic probe is introduced, positioned and frost-fixed after filling the bladder with air, the latter insulating the vesical walls from the freeze tip; a KUB film confirms the air cystogram and probe position. Now, *that tissue which is cooled the fastest is most completely destroyed;*[10] therefore, rapid freeze to −160°C. or lower is effected. Throughout this operation thermocouples monitor the rectal wall and prostatic lobe temperatures; a finger is kept continuously in the rectum to apply avascularizing digital counterpressure against the asymmetrically prominent parts of the prostate and, more important, to ascertain that the rectal wall remains freely moveable. At the conclusion of the freeze (average time 8 minutes, with range of 3-30 to achieve prostatic tissue temperature of −20°C.) rapid warming is carried out within two minutes and No. 18 Fr. Foley catheter drainage is instituted and maintained for one week.

Cryogenic prostatectomy is thus particularly suitable for the poor-risk patient who may have advanced prostatic malignancy or bleeding disorder because there is less need for prolonged anesthesia, minimal blood loss, little postoperative pain and morbidity and an acceptably low mortality. The application of cold has certain obvious advantages: it is, in itself, anesthetic as well as hemostatic; its action is predictable, controllable and reversible in certain temperature ranges; despite its fantastically destructive action, it is very well tolerated.

What, then, are the disadvantages? The most significant is a tendency toward prolonged catheter drainage with occasional difficulty in the management of tissue slough; this may require transurethral instrumental removal. The amount of slough is proportional to the abundance of non-glandular fibromuscular stroma, since the adenomatous glandular tissue itself liquefies quite readily. A collagen solvent will hopefully obviate this problem in the future.

Report Of Cases

There were 13 patients in this small, short-term series and the average age was 77 years (youngest, 66; oldest, 86); the first was operated in September, 1966 and the most recent in mid-February, 1967. There was one postoperative death:

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* Manufactured by Union Carbide Corp., Linde Division.

a 75 year-old man who had been denied cryosurgery on two earlier hospitalizations in the previous seven months because of cardiac and renal insufficiency died suddenly on the day after operation; the probable cause of death was myocardial infarct (no autopsy obtained).

All patients underwent preliminary medical evaluation; the average hospital stay after cryoprostatectomy was 12 days. Ten of the 13 patients required catheter drainage on admission to hospital for relief of complete obstruction (one 86 year-old patient had worn a catheter for two years and nine months prior to operation). Three of the thirteen developed transient azotemia postoperatively (all 3 had required catheter drainage before admission for relief of renal insufficiency).

The serum acid and alkaline phosphatase levels were determined preoperatively and for three consecutive days after freeze. In all cases but one the acid phosphatase rose sharply within a day or two after cryosurgery and then quickly returned to normal; the alkaline phosphatase was not affected. The serum LDH activity was increased in all patients postoperatively, as expected. Four men had fever (temperature higher than 100.5 degrees) after the procedure.

The most distressing complication was Gram-negative septicemia in three patients, on the 1st, 4th and 28th days after operation; all men had had positive urine cultures before the freeze (one of the three had never been catheterized) and the blood cultures yielded the same organism (E. coli, enterococcus). The patients in this series with this particular complication were not critically ill, despite the potential seriousness of the event; fortunately, all three episodes were short-lived and the men recovered promptly without recourse to heroic measures. Five of the patients required re-insertion of the catheter for further drainage and lavage of necrotic debris.

The average duration of freeze at −160° C. or lower was 10½ minutes. Four of the 13 patients had histologically proven advanced carcinoma of the prostate. The size of the prostate was graded as follows (clinical and endoscopic evaluation): four-plus in 2 (carcinoma with local extension), three-plus in 6, two-plus in 3 and one-plus in 2. Two of the men required transurethral removal of necrotic tissue, one at 4 and another at 7 weeks after operation.

There have been no strictures or contractures to date; pyuria has persisted for two to three months. None of the patients developed epididymitis, incontinence, rectal complications, bladder perforation, penile edema, osteitis pubis or postoperative hemorrhage; no blood transfusions were necessary.

One patient with carcinoma underwent needle prostatic biopsy seven weeks after operation; this yielded necrotic tissue only. "It has been suggested that the remnants of tumor left after freezing and thawing may produce an immunizing agent or autovaccine that might be effective against further cancer growth in the patient; immunologic studies investigating this possibility are currently under way."[2] At the same time, changes in the denaturization of human tissue might cause a foreign protein type of reaction;[10] therefore, until more information is available regarding immune responses, cryogenic ablative surgery must not be repeated in the same patient.

Summary And Conclusions

The history and development of cryogenic surgery are reviewed and the pathologic findings summarized; the equipment and technic are described. A preliminary report of thirteen cases is presented. Cryogenic prostatectomy is an acceptable method for relief of bladder outlet obstruction and seems to be particularly suitable for the poor-risk patient who may have advanced prostatic malignancy or bleeding disorder.

Addendum And Comment

Since submission of this report, ten more cryogenic prostatectomies have been performed, bringing the total number in the series to twenty-three (as of October 17, 1967).

To reiterate, in this series cryogenic prostatectomy has been performed exclusively in poor-risk patients who could not tolerate a more formidable procedure for relief of bladder outlet obstruction.

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THE PRESIDENT'S PAGE

THANKSGIVING DAY

Four wild turkeys played an important part in the Plymouth Colony's celebration 346 years ago when Governor William Bradford proclaimed a day of thanksgiving for surviving and recovering from a winter of privation. After the Revolutionary War the first national Thanksgiving Day, proclaimed by President Washington, was on November 26, 1789. In 1863 with preservation of the Union in sight, Abraham Lincoln revived Thanksgiving Day. There have been threats to security, threats to independence, threats to the dignity of the individual. The challenge has been met aggressively, and later appreciation for the stumbling awkward accomplishment has been forthcoming.

Let thanks be given today in 1967 when each person can assert his individuality. He can hire whoever will work for him. He can work for whoever will hire him. He can buy bread at one store and his neighbor can at another, or vice versa. He can select his own physician and hospital under a system of medical care unexcelled in the world. He can resist the trend toward centralization of control, toward the stifling of initiative by the domination of bureaucracy. The socialistic elements in our government demonstrate utter disregard for actual tax costs and scant concern for the true needs of the public. The political effect seems more important than the socio-environmental result. This does not mean that government cannot be helpful and assume a proper burden in the care of the public, including the health care.

Truly a deep canyon lies between its diametric actions and contradictions. On the north rim is heard the bleating cry for more practicing physicians and nurses and schools to train them. The south rim resounds with the hawking of multitudinous and opulent grants for research and "planning." These may divert some physicians from practice to the laboratory. They certainly help support some medical schools and accentuate the precept—already over-weighted—that students should enter investigative or at least academic medicine. Scholarships are offered practicing nurses to seek Ph.D. degrees. Doctors and nurses are thus diverted from patient care. The Heart, Cancer and Stroke law was destined to concentrate knowledge—and patients—in a few centers. Fortunately efforts by the AMA reversed the direction, steering education to the practicing physician for the patient locally.

The future looks brighter. The Yale medical students have been introduced to the subject of "Federal Government and the Physician" in a ten-lecture course. I trust the few vociferous advocates of government subsidy and control do not represent all the medical students! But at least they are thinking. Students elsewhere have spent summers improving care in the ghettos and savouring the sweet-and-sour taste of practice. Even in England, where our forerunners' "universalization of welfare services" has wrought financial havoc, a recent poll reported by the Institute of Economic Affairs indicates that 96 per cent of the British prefer to select their own doctor. How open are our eyes—physicians and public alike—to the trends, problems and failures in other countries? How alert are we to each small insinuation of the termites in our own house? Will we Americans in our generation meet our threats and challenges aggressively and effectively block the inroad of government into the practice of medicine?

Let us work among ourselves, or *with* government—certainly not *for* it—in the best interest of our patients. And for this privilege let us be thankful.

E. Tremain Bradley, M.D.

FROM THE GENERAL MANAGER'S OFFICE

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CALL

SEMI-ANNUAL MEETING OF THE HOUSE OF DELEGATES

The 1967 Semi-Annual Meeting of the House of Delegates will be held at the Holiday Inn, 404 Bridge Street, Groton, commencing at 2:00 o'clock in the afternoon of Wednesday, December 13.

E. Tremain Bradley, President
Kenneth F. Brandon, Speaker of the House
Charles Polivy, Secretary

INTRODUCTION OF RESOLUTIONS

Article V, Section 12, Par. 3 of the Bylaws of the Society Provides that:

All resolutions to be considered as regular business at any regular meeting of the House of Delegates must be in the hands of the Speaker not later than seventy-two hours before the opening of that meeting. All resolutions and recommendations published in the official agenda distributed to the members of the House prior to the meeting at which action is to be taken shall be considered as regular business. Resolutions presented later than seventy-two hours before the opening of a meeting will be referred for consideration as regular business by the House only when they are presented by the Council or accepted for consideration by majority vote of the delegates present. Any resolution which does not qualify in accordance with the aforesaid provisions for consideration as regular business may be accepted for action by a majority vote of the delegates present and, if so accepted, shall be referred at once by the Speaker to a reference committee. Any such reference committee shall consider resolutions referred to it and shall report, with recommendations to the House before adjournment of the meeting.

PROPOSED AMENDMENTS TO THE BYLAWS

The following proposed amendments to the Bylaws were presented to the House of Delegates on April 25, 1967 and were tabled for consideration and action at the next regular meeting of the House of Delegates.

In accordance with the Bylaws, these amendments will be published in Connecticut Medicine, "on one or more occasions prior to the next meeting . . . at which meeting the amendment shall be taken off the table and acted upon by the House of Delegates."

INTRODUCED BY THE COUNCIL

RE: ESTABLISHMENT OF A JUDICIAL COMMITTEE AND OUTLINING PROCEDURES PERTAINING TO SAME.

PROPOSED AMENDMENT

Article VII—The Council.

Section 1. Powers and Duties.

Par. 4. Censorship: The Judicial Committee shall be the Board of Censors of the Society. All questions of an ethical nature brought before the House of Delegates or a general meeting shall be referred to the Judicial Committee without discussion. It shall hear and decide all questions of discipline affecting the conduct of members of component associations on which an appeal is taken, and its decision in all such matters shall be final.

The Judicial Committee shall serve as a board of review from cases of claimed malpractice referred to it by the committee on medical ethics and deportment of any component county associations.

PRESENT BYLAW

Article VII—The Council.

Section 1. Powers and Duties

Par. 4—Censorship.

"The Council shall be the Board of Censors of the Society. It shall consider all questions involving the rights and standing of members in relation to other members, to the component associations, or to this Society. In addition, all questions of an ethical

nature brought before the House of Delegates or a general meeting, shall be referred to the Council without discussion. It shall hear and decide all questions of discipline affecting the conduct of members of component associations on which an appeal is taken, but only on questions of law and procedure and not on facts and its decision on all such matters will be final.

(a) The Council shall consider only the records of the component medical association in the proceedings involved.

(b) It shall determine that the record available to them is material and sufficient to support the findings which the component medical association reached.

(c) If determining that the above procedure was correct, it shall make its findings known to the appellant.

(d) If, however, finding that the procedure was not material or sufficient, it shall remand the case to the component medical association and ask for a new hearing.

(e) No appeal shall be considered or reviewed until such time as the component medical association has made its decision as to the facts in the case.

The Council shall also serve as a board of review for cases of claimed malpractice referred to it by the committee on medical ethics and deportment of any component county association."

PROPOSED AMENDMENTS

Article X—Committees of the Council.

Section 1. No change.

Section 2. Standing Committees of the Council.

Par. 1. Outline

Change "A Committee on Preliminary Study of Censorship Questions" to read "A Judicial Committee"

Par. 2. Membership. The members of all standing committees of the Council shall be discharged automatically upon the adjournment of the annual meeting of the House of Delegates following their election except for the Judicial Committee.

Par. 7. Committee on Preliminary Study of Censorship Questions (delete and insert the following:)

Par. 7. Judicial Committee

a. Composition. The Judicial Committee shall consist of twelve members of the Society. Each must have been a member of the Society for 10 years and have served as an officer of the Society or of a component association. Initially, the Council shall elect one member from each component association and four members-at-large each to serve until his seat is filled by Council election in one, two, three, or four years. Annually, thereafter, the Council shall elect one member from each of two component associations in quadrennial rotation, and one member-at-large, each to serve a four year term. No member shall serve more than two consecutive terms. The Council shall appoint the Chairman for a term of two years but shall not reappoint the same Chairman more than twice in succession.

b. Jurisdiction: The judicial power of CSMS shall be vested in the Judicial Committee, with jurisdiction over all members of the CSMS, acting within its functions. Its decision shall be final and binding, except that members of the AMA shall have those rights of AMA members. In case of appeal to the AMA, any decision shall be stayed until such procedures have been exhausted according to the AMA Constitution.

c. (1) Functions: To interpret all questions of medical ethics. The Judicial Committee may study and render an opinion when indicated on any question referred to it from the Council or from any other responsible source on its own motion involving the rights, standing, or obligations of members in relation to other members or to the component association or to the Society or any subdivision thereof, or on any question of an ethical nature or affecting the good name of the profession, or on any appeal of a question of discipline affecting the conduct of a member of a component association, or on any litigation arising out of a physician's practice. Its opinions shall be binding on the parties concerned and specific problem considered, but shall be considered only as a presumption of the Society, binding on all members only when endorsed by the Council and published in "Connecticut Medicine". The Judicial Committee may use its judgment whether or not to request such endorsement from the Council.

(2) To interpret the Constitution (Charter), Bylaws and Rules of CSMS and the component county associations: to decide any dispute or questions between the CSMS and county association, or between county associations.

(3) Investigating Jury: The Judicial Committee, acting on its own motion or on request from any responsible source, may request the President to appoint a jury to investigate and report on any complaint or condition in the state of greater than local concern affecting the profession as a whole. If the jury finds that there is probable cause for action, it shall so state. The President shall in turn submit the report to the Judicial Committee. If it agrees that there is need for action, it shall first request the county medical society having

jurisdiction to take appropriate action and to submit a report of the facts found and the action taken. The Judicial Committee may act in its appellate function as to any action taken by the county in the matter.

(4) The Judicial Committee shall represent the Society on the Physician-Hospital Mediation panel. The chairman may appoint an ad hoc subcommittee of three members, who shall be impartial as to subject matter, persons involved and other prejudicial factors, to assist in resolving disagreements involving members of the Society when those procedures recommended by the Joint Commission on Accreditation of Hospitals have failed.

(5) The Judicial Committee shall render an annual report to the Council including its actions, opinions, and recommendations and shall make such interim reports as it desires or as are requested by the Council. Such reports shall be available to members of CSMS.

d. Procedure: A majority shall constitute a quorum. The Committee shall meet at least bimonthly. The President shall fill any vacancy. The Committee, in any ethical problem, which in its judgment transcends medical ethics, may invite discussants and participants, lay as well as medical.

PRESENT BYLAW

Par. 7. Committee on Preliminary Study of Censorship Questions. *When the Council receives a question involving the rights and standings of members, in relation to other members or to the component associations or to The Society, or when a question of an ethical nature is referred to the Council from the House of Delegates, or when an appeal is taken to the Council on a question of discipline affecting the conduct of members of component associations, or when a case of claimed malpractice is referred to the Council by the committee on medical ethics and deportment of a component association, the Council shall elect a Committee on Preliminary Study of Censorship Questions which shall study and review such question or appeal or claimed malpractice case and shall report its findings and recommendations to the Council. Once such committee is elected, it shall serve as a standing committee of the Council.*

PROPOSED AMENDMENT

Article XIV—Component Association

Section 7. Discipline

Par. 1. Appeal

Any member of the Society aggrieved by disciplinary action of the component association of which he is a member shall have the right of appeal to the Judicial Committee of the Society, which shall review the proceedings and render a decision concerning the disciplinary action taken; this shall be final, in its jurisdiction, except that members of the American Medical Association may appeal to the Judicial Council of the AMA.

Par. 2. Procedure

Procedure: An appeal shall be in writing, signed by the appellant. The appellant must send (within ten (10) days of notice of the decision) a copy of his intent to appeal to the Secretary of his Association, and to the General Manager of the Society who shall immediately notify the Chairman of the Judicial Committee. The County Association shall then prepare a concise summary of the case, giving the charges, the relevant facts found in the hearing, and the principle of ethics of which the accused was found guilty of violating. It shall send a copy to the appellant and to the Judicial Committee within thirty (30) days of the appellant's letter of intent to appeal. The appellant shall send a copy of his brief to the General Manager for the Judicial Committee, and to the Secretary of his Association; specifying the procedures, findings of fact, conclusions or disciplinary action or any part thereof that is questioned or challenged within thirty (30) days of the date the County Association has sent a copy of its summary to him. All unchallenged evidence or matter material to the charges in the proceedings shall be presumed to be accepted and admitted as factual. On request by the Judicial Committee the Association shall furnish all records (or copies) of the proceedings and other pertinent material. Such records shall be made available to the defendant. The Committee may remand either brief to the appropriate party with instructions.

The filing of an appeal shall automatically stay the execution of the original decision until all the appeals including one to the AMA, shall have been acted upon. Appeals to the AMA must be made in accordance with their rules.

The Judicial Committee may restrict itself to the issues raised in the briefs and make its decision thereon. But if either party requests to appear in person, both parties shall be invited to appear before the Judicial Committee after proper notice, not less than ten (10) nor more than thirty (30) days. Each party shall be entitled, upon application and for cause shown, to reasonable adjournment of such a hearing.

The Judicial Committee may limit the proceedings to the oral argument, relevant and supplementary to their briefs, allotting thirty (30) minutes for each party, or may extend the hearing on request or on its own initiative, by majority vote, as long as necessary to insure that its verdict is just and fair.

It shall not be the purpose of the Judicial Committee to re-try the case but rather to determine that the hearing by the county was fair. It shall have appellate jurisdiction in questions of law and procedure, only setting aside questions of fact when, in its opinion, such findings are not supported by a preponderance of evidence. Under exceptional circumstances and at its own discretion, the Committee may call up witnesses and elicit such testimony as may be considered necessary to arrive at a fair and considered judgment. It may remand the case to the Association with instructions whenever or for any part of the proceedings it decides necessary.

The Committee is authorized to use legal counsel. The defendant may be represented by a member of the Society and/or be accompanied by legal counsel who may advise but not participate in the proceedings. The defendant may enter objections in the course of the proceedings. The appellant may be assisted in preparing his brief and appeal. The Committee shall not be bound by legal rules of evidence.

The members of the Judicial Committee shall be impartial to the parties and to the substance of the charges. If anyone shall disqualify himself or be disqualified for cause on challenge, the President of the Society shall appoint a substitute.

If either party shall refuse to cooperate or fail to appear without cause, acceptable to the Committee, the Committee may proceed, dismiss, or decide the case. The Committee may request any member of the Society to appear and answer reasonable questions; refusal or failure without cause acceptable to the Committee to cooperate shall be considered unprofessional conduct.

The Judicial Committee shall decide by written ballot. Only those present throughout the hearing shall vote; a majority shall be necessary to overrule the County. It shall vote first on the decision as to guilt; then as to the penalty. It may affirm or reverse the verdict, and modify the penalty or make such other disposition as it deems proper. It shall notify the parties of its decision by registered mail within ten (10) days of completion of the hearing.

Any member of the Society, in any proceeding before any committee or association of the Society or component thereof, which is disciplinary in character or might reflect in any manner on his honor or reputation as a physician or person, shall be entitled to the following principles of fairness and procedure, reasonably detailed in practice: notice, written charges, a hearing before an impartial tribunal, the right to be present throughout the hearing, to reasonably cross-examine witnesses, to present witnesses and other reasonable means to defend himself, the right to be represented by a medical colleague and to be advised by legal counsel. The Judicial Committee of the Society shall require, in any appeal, that the previous proceedings have been conducted in a manner consistent with the principles of justice herein above expressed.

All dates shall be considered post-dates.

The Judicial Committee shall complete an appeal and notify the parties within four (4) months of the appellant's letter of intent to appeal.

PRESENT BYLAW

Section 7. Discipline

Any member of a component association who is aggrieved by disciplinary action of the component association of which he is a member shall have the privilege of appealing to the Council of the Society which shall review the charges made against the disciplined member and the findings therein and render a decision concerning the disciplinary action taken; this shall be final.

SUMMARY OF ACTIONS COUNCIL MEETING

Thursday, September 14, 1967

I. Attendance

Present in addition to the Chairman, Dr. Stevens J. Martin, were: Drs. Bradley, Gardner, Grendon, Polivy, Brandon, M. Caplan, Fabro, Hess, Rogol, Cramer, Abbot, Spitz, Johnson, Pelz and Roch. Also present were: Mrs. Lindquist, Mr. Villano, Mr. Norbeck (AMA), Dr. Thayer (Chairman of Committee on State Blood Bank) and Dr. Richards. Absent were: Drs. H. Caplan, Egan, Hastings, Shepard, Ayres, Nolan, Jacobson, Jr., Grant, Petrie, Wilson and Palomba.

II. Routine Business

Life Memberships

It was VOTED to approve applications for Life Membership received from the following eligible Active Members:

Mary Adams, Port Chester, New York (FCMA) —1967

Norton Canfield, St. Croix, Virgin Islands (NHCMA)—1968

Michael A. Conroy, Meriden (NHCMA)—1967

Harold A. Flynn, New Haven (NHCMA)—1968

Date Of Next Meeting

The next Council meeting is scheduled for Wednesday, October 18, 1967.

III. Old, New And Special Business

Date And Site Of 1967 Semi-Annual Meeting, House Of Delegates

It was VOTED to accept, tentatively, the invitation of the FCMA Councilor to hold the semiannual meeting of the House of Delegates in Fairfield County in December, *unless* the New London Association elected to ask that the meeting be held in its area. Such an invitation has since been received from the officers of NLCMA, and the meeting of the House will be arranged for December 13, at Groton, Connecticut.

New Format for 1968 Annual Meeting

On July 26, the Council approved an "outline" for the 1968 Annual Meeting of the House of Delegates and Scientific Assembly. At this meeting, it was VOTED to approve the detailed format and scheduling for the three-day session at the Hartford Hilton Hotel, Hartford. A motion (introduced by the Board of Directors of HCMA) to have the Council reconsider its July 26 decision re spreading the meeting of the House of Delegates over two days was lost.

It was further VOTED to inform the officers of the component county medical associations of the changes in plans from prior years, and to urge their cooperation and that of their Delegates to CSMS in giving the new format full opportunity to prove its merits.

Resignation—Vice-Speaker Of House Of Delegates

It was VOTED to accept, with regret, and thanks for previous service, the resignation of Henry Caplan, Yalesville, as Vice-Speaker of the House of Delegates. It was further VOTED to appoint Frank K. Abbot, Waterbury, to replace Dr. Caplan in this post for the balance of the 1967-68 term, such appointment to be transmitted to the House of Delegates in December for confirmation.

It was further VOTED to accept Dr. Caplan's resignation as a member of the following committees: Committee on Hospitals, Committee on Publications, Advisory Committee to State Commissioners of Welfare, Finance and Control, Council's Committee on Preliminary Study of Censorship Questions. Advisory Committee (to State Health Dept.) on Cardiovascular Diseases, and the CSMS Panel for Physician-Hospital Mediation. The New Haven Association will be requested to furnish a replacement on the last-named Panel.

Report—Committee On National Legislation

It was VOTED to accept, with commendation, a report submitted by the Committee on National Legislation on the July expedition which five members of the Committee made to Washington, D.C. to visit with the Senators and Representatives from Connecticut in the 90th Congress. In general, the members who went felt that the visits were rewarding bilaterally and that they should be repeated in the future.

It was further VOTED to accept a series of recommendations made by the Committee, by acting upon them separately as follows:

(1) To request the Committee on Hospitals to undertake additional studies of hospital costs.

(2) To authorize the assignment of members of the Committee on National Legislation by its Chairman to maintain liaison with each of Connecticut's national legislators, and to promote the formation of local-level subcommittees to participate in such liaison.

(3) That the Committee, with assistance from the Society's staff, prepare a list of physicians interested in environmental medicine and medical instrument technology, such list to be furnished Rep. Daddario (at his request).

(4) That Rep. Giaimo be furnished with a list of the physician members of the CSMS Conference Committee with the Connecticut Bar Association, and that he be sent a letter of thanks for placing in the Congressional Record a statement on Project Viet Nam (recruitment of physician volunteers for service to civilian casualties of war).

(5) That the Committee draw up plans, including cost estimates, for an "annual dinner" for Connecticut Senators and Representatives, and submit same to the Council for prior approval.

(6) That the AMA's Chicago and Washington, D.C. offices be kept informed of activities of the Society in the field of national legislation.

(7) That plans for similar "expeditions" to Washington, D.C. be drawn up by the Committee, at such intervals as seem appropriate, and be submitted to the Council for prior approval.

Report—Legality Of Telephone Prescribing Of Narcotics

Pursuant to actions taken by the Council at the July 26 meeting, reports on this subject were received as follows:

(a) State Health Commissioner Foote advises (via a ruling of the State's Attorney General) that the telephone prescribing of Class A Narcotics by physicians is prohibited by Federal regulation and that, hence, statutes enacted by the 1967 General Assembly which apparently legalized such prescribing have no legal standing whatever at the present time.

(b) The AMA Department of Medical Ethics states (in brief) that while the Federal regulations may cause "occasional inconvenience on the part of either the patient or the physician," the 1966 Interim Session of the AMA House of Delegates found that "this is not sufficient to warrant . . . changes (being sought) in the Harrison Narcotics Act" to legalize telephone prescribing, thereby opening possible avenues of abuse by addicts and illegal traffic in narcotic drugs.

It was VOTED to publish this information in the Journal.

Reports Of The President

The President, E. Tremain Bradley, presented reports as follows:

(a) As requested by the Council, he has had several discussions with the President of the Connecticut State Dental Association concerning improved working liaison between the two organizations at administration level with respect to matters of mutual interest. A final report, with recommendations, will follow in the near future.

(b) It was VOTED to refer to the Committee on Mental Health, for study and recommendation, a request of U.S. Bureau of Drug Abuse Control that the AMA and its constituent state (and component county) medical societies "encourage discussion . . . of drug abuse problems, as an added educational function" of the organizations. The Bureau will furnish material, visual aids and personnel to help the societies plan such discussions.

Confirmation Of Nominations

It was VOTED to confirm the nominations to the Governor for appointment to the Committee to Study the Need of Family Physicians (S.A. No. 371) of the following members:

Gaert S. Gudernatch, Sharon
Ralph L. Gilman, Storrs

Joined by representatives of the General Assembly, State Commissions, the Connecticut Academy of General Practice, the Connecticut Society of American Board Internists and others, the CSMS nominees will form a Committee to study the need for more family physicians in the State, and evaluate existing and proposed methods of encouraging medical school graduates to pursue careers in family practice.

It was further VOTED to submit the name of Donald B. Alderman, New Haven, as an alternate nominee in the event that Dr. Gilman or Dr. Gudernatch is unable to accept appointment to the Study Committee; also to nominate Drs. Gilman and Gudernatch for appointment to the Taskforce on Manpower of the Regional Medical Program.

Request—Committee On State Blood Bank

John E. Thayer, Hartford, joined the Council to present the problem of blood being classified by law as a "commodity" instead of a medical service, thereby subjecting it to stringent requirements of guaranteed purity, etc. It was VOTED to approve, in principle, the concept that blood used for transfusion is a medical service, and to direct the Committee on State Legislation to prepare and submit a bill (modelled after bills successfully introduced and passed in other states) at the 1969 General Assembly to establish this concept by law. Dr. Thayer and the members of the Committee on State Blood Bank will be available to testify in support of such a bill at the appropriate time. It was further VOTED to instruct the Society's AMA Delegates to introduce a resolution at the November meeting of the AMA House of Delegates asking for national support of the subject concept.

Report—Mail Balloting On Extending ODMC Agreement

It was VOTED to receive as information the results of the August balloting (by mail) on the question of extending the 1965 agreement with the Office of Dependents' Medical Care Program from July 31, 1967 to November 1, 1967, in order for Connecticut General to have sufficient time to make arrangements to take over the administration of the Program (from Connecticut Medical Service, Inc.) and to operate it on a usual and customary charge basis. Twenty-six votes were cast. The tally: Yes-25; No-1. The agreement has been extended.

Request—Authorization To Form Section On Thoracic And Cardiovascular Surgery

It was VOTED to approve a request received from a group of CSMS members to form a Section on Thoracic and Cardiovascular Surgery, and to recommend to the December meeting of the House of Delegates that authorization to form such a Section be granted, *provided* that the proposed bylaws submitted are amended to conform with the bylaws of the Society as to members of the Section being privileged to vote and to hold office. It is understood that this amendment is agreeable to the group making the request.

Reports On Implementation Of Title XIX Program

(a) It was VOTED to receive as information a report of the Advisory Committee to the State Commissioners of Welfare, Finance and Control concerning an August 17 meeting with the Commissioners on the subject of the fee schedule and claims procedures to be followed by physicians under Title XIX from October 1, 1967 to March 1, 1968 (when a "usual and customary charge" method of payment will be put into effect). It was further VOTED to adopt a resolution recommended by the Advisory Committee which reads as follows:

Whereas: The CSMS Advisory Committee to the State Commissioners of Welfare, Finance and Control has met with Commissioner Shapiro, and has determined that he does not contemplate establishing a new uniform fee schedule for physicians' services under Title XIX for the period October 1, 1967 to March 1, 1968; and

Whereas: The Council and House of Delegates of CSMS have disapproved the use of any uniform fee schedule in the implementation of Title XIX, of whatever type and by whatever name; therefore be it

Resolved: That the Council of CSMS *not* act to obtain a new uniform fee schedule for physicians' services under Title XIX for the period October 1, 1967 to March 1, 1968, but, instead, continue to seek to implement the "usual and customary charge" principle under Title XIX in a sound and equitable manner.

(b) It was VOTED to receive as information, a report filed by Sidney L. Cramer, Hartford, CSMS representative on the Title XIX Professional Advisory Committee, on the proceedings of the first meeting of that Committee on September 1, 1967. In brief, Dr. Cramer reported that, while the statute enacted by the 1967 General Assembly authorizes a "new" uniform fee schedule to be applied to payment for physicians' services prior to the start of "usual and customary charges" on March 1, 1968, it is the intention of the Professional Policy Committee (Commissioner Shapiro and Conkling) to continue the "old" (existing) schedule until next March 1, but that most other healing arts professions had submitted proposed uniform fee schedules for approval by the Professional Policy Committee. In conclusion, Dr. Cramer stated that he had not offered any schedule on behalf of the Society, and asked for Council direction as to what course he should pursue at future meetings of the PAC. In replying to this request for guidance, the Council suggested that Dr. Cramer be guided by the resolution adopted under (a) of this item. (AMB 9/14/67 "G")

(c) The President, E. Tremain Bradley, offered primary and supplementary information on previous items (a) and (b). He also attended the September 1 meeting of the Professional Advisory Committee (having been appointed as a citizen-member by Commissioner Shapiro), and confirmed much of what Dr. Cramer had reported. In addition, he recommended that the Society *not* take steps to obtain a new fee schedule for the period October 1, 1967-March 1, 1968, but make every effort to assure a workable usual and customary charge method later on and keep the membership informed concerning same.

Request—Connecticut Hospital Association

As requested by the CHA, it was VOTED to endorse the content of a document titled: "Suggested Guidelines of Relationship Between Hospitals and the News Service Media," which had been drafted for the Council on Administrative Practice of CHA. It was further VOTED to suggest to CHA that the inclusion of more detailed guidelines applying to Emergency Rooms (particularly "after-hours") would make the document more complete and helpful.

Question—Payment For Physicians' Reports in Legal Cases

It was VOTED to refer to the Conference Committee with the Connecticut Bar Association for study, report and recommendation, the question of procedures that should be understood and followed by both physicians and attorneys in the matter of payment to the physician for medical reports furnished at the request of the attorney; i.e., should payment be made in advance, upon delivery, or on a billing basis—and by whom? The question originated in the Fairfield County area, but was felt to be of statewide interest.

Review—New Third Party Payment Proposal

It having been reported that Connecticut Medical Service, Inc. will soon implement a new "Century" contract, it was VOTED to request the Committee on Third Party Payments to examine said contract and to advise the Society concerning it (in accordance with the CSMS bylaws). While the Society no longer has any official connection with CMS, it is felt to be desirable for the Society to keep abreast of all current developments in the prepayment field and to determine the extent to which the newer proposals accommodate the CSMS policy on "usual and customary charges" as the preferred basis of payment for physicians' services.

Follow-up On July Seminar On County Review Committees

As planned previously, the transcript of the proceedings of this Seminar on the purposes and functioning of county medical association review committees (for review of claims for payment for physicians' services) will be edited and published in the Journal as information for the membership. There was general agreement among the members of the Council that the "question and answer" periods that followed each presentation at the Seminar suggested that there exists a disparity of opinion among individuals and among the county associations as to just what questions a review committee should handle as well as how it should handle any or all questions. It was therefore VOTED to request the President to appoint an Ad Hoc Committee, to include members of the Liaison Committee with Connecticut General on Medicare B, which Committee shall review the transcribed proceedings of the July Seminar and make recommendations to the Council concerning the Society's present guidelines for county review committee operation and for possible changes to be made in same.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on September 14, 1967. Detailed minutes of the meeting are on file at 160 Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT WANTED

SURGEON — Board certified in General and Thoracic Surgery wishes a group or associate type practice in a coastal town. Interested in peripheral vascular, cardiac and thoracic surgery. Has applied for Connecticut license. Military obligations completed.

SURGEON—39 years of age, Board eligible, Connecticut license. Wishes to practice in a group or associate practice in Connecticut with no preference to town. Available immediately. No military obligations.

OBS-GYN—Board certified, 33 years of age. Presently completing military obligations. Would like to enter into a group or associate practice. Available February 1, 1968.

G.P.—30 years of age, military obligations completed. Wishes to practice in a group, and will be available on or about November 1, 1967. Excellent training and background.

PATHOLOGIST—34 years of age, Board eligible, Connecticut license. Interested in Associate pathological practice. Excellent background and training. Available November, 1967.

PLACEMENT OPPORTUNITIES

WANTED — young internist, Board eligible or certified to associate with two other young internists in modern, fully equipped building in suburb of Hartford.

PSYCHIATRIST — challenging position open at modern Connecticut penal institution. Opportunity to organize and develop treatment program. Salary range up to $20,500. Outstanding retirement and fringe benefits. Must have three years' residency training in a center acceptable by American Board of Psychiatry and Neurology and a year as staff psychiatrist; eligible for Connecticut license. Write: S. Stein, State Personnel Department, 405 State Office Building, Hartford, Connecticut 06115.

INTERNIST — to act as consultant to medical profession, hospital and nursing home administrators to assure creation and effective functioning of hospital services for participation in the Hospital Insurance Program; assists with formation of utilization review committees and reviews proposed plans of hospital and extended care facilities; surveys institutions participating in the Health Insurance for the Aged Program and provides professional guidance to a medical staff, administrators, and owners concerning medical records, policies, and utilization review plans; evaluates medical staff organization; participates in educational programs for professional and sub-professional staff of health care facilities; prepares and studies reports. Excellent salary, good fringe benefits and retirement program. Contact: State Personnel Department, State Office Building, Hartford, Connecticut 06115 for further information.

HOUSE PHYSICIAN — Diversified duties in accredited, voluntary hospital. Connecticut license required. Monday through Friday, every other Saturday morning. $18,000 a year. Write: P.O. Box 3474, Bridgeport, Connecticut 06604.

PATHOLOGIST — full time or part time, to direct a clinical laboratory in an 1800-bed mental hospital. Ample opportunity for research and teaching available. Well equipped and staffed laboratory. Emphasis on Neuropathology. Board certified or eligible pathologist preferred. Starting salary range: $16,460-$19,760. Excellent fringe benefits. All particulars in first letter, including references. Contact: Mehadin K. Arafeh, M.D., Superintendent, Connecticut Valley Hospital, Box 351, Middletown, Connecticut 06458.

Increased participation by members of the Connecticut State Medical Society in the Society Sponsored Overhead Expense Plan, plus continued favorable experience, has resulted in a rate reduction of 12%, effective November 1, 1967. Underwriting limits have also been raised from $1,000 to $1,500 a month. A continuous program of expanding benefits since 1961 made this the broadest benefit Overhead Expense Policy on the market; these latest changes, however, make this plan incomparable. For details write: Group Insurers, Inc., 1184 Chapel Street, New Haven, Connecticut 624-2121

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PATHOLOGIST — State of Connecticut centrally located general hospital. Must have two years' employment in pathology; be eligible for Connecticut license. Salary range: $16,460-$22,180 plus many extras. Write: S. Stein, State Personnel Department, 405 State Office Building, Hartford, Connecticut 06115.

ANESTHESIOLOGIST — Board eligible or certified to join small partnership in private practice at the Windham Community Memorial Hospital, 112 Mansfield Avenue, Willimantic, Connecticut 06226. A progressive growing hospital in a community with a State College and the University of Connecticut only 8 miles away. For further information, contact William Grillo, M.D. or Samuel Dodd, M.D. at the Windham Community Memorial Hospital, Willimantic, Connecticut — Telephone 423-9201.

PEDIATRICIAN urgently needed for community 15 minutes from Hartford with population area of 45,000 people. Opportunity available to head Pediatrics Department in hospital undergoing extensive construction program. Congenial medical staff will help establish. Write: Secretary, Medical Staff, Rockville General Hospital, Rockville, Connecticut 06066.

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WELL ESTABLISHED ORTHOPEDIC PRACTICE for sale; excellent equipment; office near major New Haven hospitals; complete files containing case histories and many legal liability matters. Gross $45,000-$50,000 yearly.

WANTED—qualified family doctor to take over my practice 30 minutes from Hartford. No obstetrics or orthopedics. Expense-sharing and coverage arrangement with M.D. in same office building. Nearby lab and x-ray. Low price for equipment. No charge for goodwill and introductions. Leaving to specialize. Contact: Lawrence S. Carlton, M.D., 64 Maple Street, Collinsville, Telephone 693-4017.

CHIEF MEDICAL OFFICER—Challenging opportunity for an experienced physician-executive to head up medical program for a large, progressive, rapid-growth corporation. Location is in mid-west, age can vary from late 30's to mid 50's. Income is open and negotiable, benefits are excellent. Company climate is stimulating.

G.P.—For limited partnership with another G.P. with eventual takeover of entire practice. Well established practice in growing town.

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1967 MEETINGS

December 13 — Semi-Annual Meeting of the House of Delegates, Holiday Inn, Groton, Connecticut, 2:00 P.M.

1968 MEETINGS

April 30-May 1-2—176th Annual Meeting of the Connecticut State Medical Society to be held at the Hartford-Hilton Hotel, Hartford, Connecticut.

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Welcome, New Members . . .

Hartford County Medical Association

Sybille von Lindeiner Brewer, M.D., St. Francis Hospital, Hartford, Connecticut 06105.

Paul Feldman, M.D., 50 Gillett Street, Hartford, Connecticut 06105.

Robert L. Fisher, M.D., 85 Jefferson Street, Hartford, Connecticut 06103.

James R. Ford, M.D., 697 Poquonock Avenue, Windsor, Connecticut 06095.

James H. Foster, M.D., Hartford Hospital, Hartford, Connecticut 06103.

Norman H. Gahm, M.D., 85 Jefferson Street, Hartford, Connecticut 06103.

Alberto J. Gambarini, M.D., St. Francis Hospital, Hartford, Connecticut 06105.

Frederick L. Geary, M.D., 350 Farmington Avenue, Hartford, Connecticut 06105.

Charles A. Gundersen, M.D., 2900 Main Street, Glastonbury, Connecticut 06033.

Teofilo G. Gutierrez, Jr., M.D., Meriden Hospital, Meriden, Connecticut 06450.

Ralph M. Lechausse, M.D., 569 East Center Street, Manchester, Connecticut 06040.

Robert L. Harris, M.D., 581 Farmington Avenue, Hartford, Connecticut 06105.

Frederic R. Keifer, M.D., One Tower Square, Hartford, Connecticut 06120.

Charles N. Leach, Jr., M.D., 1 Mill Lane, Farmington, Connecticut 06032.

Joseph P. Liss, M.D., St. Francis Hospital, Hartford, Connecticut 06105.

William Mancoll, M.D., 242 Trumbull Street, Hartford, Connecticut 06103.

George E. McGowan, M.D., 85 Jefferson Street, Hartford, Connecticut 06103.

Raymond E. Moldow, M.D., 79 Elm Street, Hartford, Connecticut 06115.

Claus P. Niemann, M.D., South Main Street, East Granby, Connecticut 06026.

Frederick B. Winston, M.D., 79 Elm Street, Hartford, Connecticut 06115.

Norman A. Zlotsky, M.D., 60 Gillett Street, Hartford, Connecticut 06105.

Fairfield County Medical Association

Anthony H. Axiotis, M.D., 71 Beach Road, Fairfield, Connecticut 06430.

Joseph G. Buchman, M.D., 17 Governor Street, Ridgefield, Connecticut 06877.

George V. Clift, M.D., 325 Reef Road, Fairfield, Connecticut 06430.

Anthony Donovan, M.D., 180 Bayberry Lane, Westport, Connecticut 06882.

Robert Fand, M.D., 8 West Street, Danbury, Connecticut 06810.

Jonathan G. Greenwald, M.D., 85 East Avenue, Norwalk, Connecticut 06851.

Ahmad Haghighat, M.D., 2820 Main Street, Bridgeport, Connecticut 06606.

Hilda C. Hanley, M.D., 2820 Main Street, Bridgeport, Connecticut 06606.

Kamal A. Hassan, M.D., 1435 Bedford Street, Stamford, Connecticut 06905.

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Paul O. Muller, M.D., Danbury Hospital, Danbury, Connecticut 06810

James P. Roach, M.D., 881 Lafayette Street, Bridgeport, Connecticut 06603.

Vincent J. Scavo, M.D., 923 East Main Street, Bridgeport, Connecticut 06608.

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Bernard V. Strauss, M.D., Arrowhead Point, Brookfield, Connecticut 06804.

Sheldon Weicholz, M.D., 675 Fairfield Woods Road, Fairfield, Connecticut 06432.

Peter J. Wick, M.D., Greenwich Hospital, Greenwich, Connecticut 06830.

David R. Widrow, M.D., 1425 Bedford Street, Stamford, Connecticut 06905.

WANT TO AVOID EMBARRASSMENT — OR WORSE?

Become Familiar With P.A. 555 — The Drug Control Law Of 1967

(The following was mailed to all licensed physicians in Connecticut by the State Departments of Health and Consumer Protection, and is reproduced in this issue to give the new drug regulations added emphasis.)

To Physicians, Dentists, Osteopaths, Veterinarians, And Pharmacists

Your attention is called to Public Act 555 enacted by the recent session of the Connecticut General Assembly which becomes effective October 1st, 1967, concerning prescriptions and record requirements for A. Controlled Drugs and B. Restricted Drugs:

A. *CONTROLLED DRUGS* classified as amphetamine-type, barbiturate-type, cannabis-type, cocaine-type, hallucinogenic, morphine-type and other stimulant and depressant drugs. By law caffeine, alcohol and nicotine are excluded.

Section 13. (a) All prescriptions for controlled drugs shall include (1) the name and address of the patient, or the name and address of the owner of an animal and the species of the animal, (2) whether the patient is an adult or a child, or his specific age, (3) the compound or preparation prescribed and the amount thereof, (4) directions for use of the medication, (5) the name and address of the prescribing practitioner and (6) the date of issuance.

(b) Prescriptions when written shall be written in ink or in indelible pencil or by typewriter. No duplicate, carbon or photographic copies and no printed or rubber-stamped orders shall be considered valid prescriptions within the meaning of this act.

(c) Prescriptions for narcotic drugs designated "Class A" under federal narcotic laws shall be signed by the prescribing practitioner at the time of issuance and previously signed orders for such narcotic drugs shall not be considered valid prescriptions within the meaning of this act.

(d) As to controlled drugs other than "Class A" narcotic drugs, a prescribing practitioner may issue an oral order and such oral order shall be promptly reduced to writing on a prescription blank and filed by the pharmacist filling it.

(f) All prescriptions for controlled drugs shall comply fully with any additional requirements of federal narcotics laws and the federal food and drug laws and the state food, drug and cosmetic laws and the regulations adopted under this act.

Section 14. (a) A pharmacist, in good faith, may sell and dispense controlled drugs to any person upon a prescription of a physician or of an osteopath, dentist or veterinarian to the extent that they are authorized to prescribe such controlled drugs. The person filling or refilling the prescription shall write the date of filling and his signature on the face of any prescription for narcotic drugs or his signature or initials on any prescription for controlled drugs other than narcotic drugs. The prescription shall be retained on file by the proprietor of the pharmacy in which it is filled for a period of three years, so as to be readily accessible for inspection by any public officer or employee engaged in the enforcement of this act. The prescription shall not be filled or refilled unless permitted by federal food and drug laws, federal narcotic laws and regulations adopted under this act.

B. *RESTRICTED DRUGS* Narcotic drugs and certain additional controlled drugs evidencing exceptional danger to health or potential abuse.

Section 17. (b) Each physician, dentist, veterinarian or other person who is authorized to administer or professionally use restricted drugs shall keep a record of such restricted drugs received by him and a record of all such restricted drugs administered, dispensed or professionally used by him. Issuance of a written or oral prescription to a pharmacist shall be deemed compliance with this section through the record made by such pharmacist. The record of restricted drugs received shall in each case show the date of receipt, the name and address of the person from whom received and the kind and quantity of restricted drugs received. The record of all restricted drugs administered, dispensed or otherwise disposed of shall show the date of administering or dispensing, the name and address of the person to whom or for whose use, or the owner and species of animal for which the drugs were administered or dispensed and the kind and quantity of drugs.

(c) Practitioners regularly engaged in dispensing controlled drugs for which they charge either separately or together with charges for other professional services shall keep a record of all controlled drugs, received and dispensed by them in accordance with the provisions of subsection (f) of this section.

(e) Pharmacies, hospitals and laboratories shall keep records of all controlled drugs, whether restricted or not, received and disposed of by them in accordance with the provisions of subsection (f) of this section.

(f) The form of record to be keept under subsection (c), (d), or (e) of this section shall in each case show the date of receipt, the name and address of the person from whom received, and the kind and quantity of controlled drugs received, or, when applicable, the kind and quantity of controlled drugs produced or removed from process of manufacture and the date of such production or removal from process of manufacture; and the record shall in each case show the proportion of controlled drugs. The record of all restricted drugs sold, administered, dispensed or otherwise disposed of shall show the date of selling, administering or dispensing, the name of the person to whom or for whose use, or the owner and species of animal for which the drugs were sold, administered or dispensed, the address of such person or owner in the instance of records of other than hospitals, and the kind and quantity of drugs. In addition, hospital records shall show the time of administering or dispensing, the prescribing physician and the nurse administering or dispensing the drug. Each such record shall be kept for a period of three years from the date of the transaction recorded. Upon the effective date of this act, a complete and accurate record of all stocks of controlled drugs on hand shall be prepared and kept on file for three years; except that if this record has already been prepared in accordance with section 511 (d) of the federal food and drug laws, no additional record shall be required, provided all records prepared thereunder shall be retained for said three-year period and shall be made available to the inspecting commissioner. The keeping of a record required by or under the federal narcotic laws, or federal food and drug laws, containing substantially the same information as is specified above, shall constitute compliance with this section, provided each record shall in addition contain a detailed list of any restricted drugs lost, destroyed or stolen, the kind and quantity of such drugs and the date of the discovery of such loss, destruction or theft and provided such record shall be made available to the inspecting commissioner or his authorized agents. The Public Health Council by regulation pursuant to section 7 may waive the kinds and forms of record keeping required of hospitals or practitioners under this section where such kinds and forms are found unnecessary for effective control under this act or where substantially the same information is equally available through other kinds and forms of record-keeping pursuant to state or federal law.

Section 19.(b) When a pharmacist sells or dispenses any controlled drug on prescription issued by a physician, osteopath, dentist or veterinarian, he shall affix, to the container in which such drug is sold or dispensed, a label showing his own name, or the name and address of the pharmacy for which he is lawfully acting, the name of the patient, or if the patient is an animal, the name of the owner of the animal and the species of the animal, the name of the physician, osteopath, dentist or veterinarian by whom the prescription was written, and such directions as may be stated on the prescription. When the drug sold or dispensed is a narcotic drug, in addition the label shall set forth the registry numbers under federal narcotic laws of both the pharmacy and the prescribing practitioner, and the address of the patient or owner of the animal and of the prescribing practitioner.

All existing provisions of the federal narcotic laws or the federal and state food and drug laws pertaining to prescriptions and the keeping of records are to be complied with.

The State Department of Health and the State Department of Consumer Protection have speakers available for professional societies wishing to obtain more details for their members. Individuals may write or call the following for further information:

Narcotic Control Section,
State Department of Health,
79 Elm Street, Hartford, Conn. 06115
Tel. 527-6341 Ext. 516

Drug Division, Department of Consumer Protection
165 Capitol Avenue, Hartford, Conn. 06115
Tel. 527-6341 Ext. 2456

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The 24th Conference of the Woman's Auxiliary to the American Medical Association for State Presidents, Presidents-elect, National Officers, and Chairmen, was held October 8-11 in Chicago at the Drake Hotel. Those attending from Connecticut were Mrs. Anthony Cipriano, President, Mrs. Clarence Harwood, President-elect, and Mrs. Norman Gardner, a director of the National Board of the Woman's Auxiliary.

There is much that YOU as a doctor's wife can do to help your husbands through your county auxiliary.

Some of the things that need our support are the AMAERF, Blood mobiles or centers where blood is collected, Education, Baby Sitters Courses, Block Mothers, Politics, Home Health Aides, Meals on Wheels and Safety.

AMAERF needs our support as the need for more doctors, better medical schools. Also the research carried on at the Bio medical laboratories at AMA Headquarters is doing great things.

Bloodmobiles or centers need volunteers to help with the collection of blood as well as to go out and get donors.

Education takes in many projects for us to do. One is to get good health education into all the schools including sex education. Under Education also comes courses teaching the children the danger of drugs, alcohol and smoking.

Baby Sitters courses are needed in many areas and your county can sponsor just such a course.

Block Mothers is a course we should encourage the P.T.A.'s to give in your elementary schools.

Politics or legislation is one of the most important roles all of the wives should be interested. This means not only to read and know what is going on in our governments but to participate in them too. We need good politicians.

Meals on Wheels is another project for us to help to get started in your area. These last two projects need help from others than just the auxiliary but you can be the group to wake up your community as to its need of these projects.

Safety too is a large project with many areas to be worked on. One is safety for School children. Are there sidewalks or personnel to help young children cross busy intersections? Are there enough traffic signals around the schools, are the busses taking children to and from school safely? All these can be projects for you. Too there is safety in the home pertaining to drugs, stairways and even equipment. As small children are not in school the home shoud be a safe place, but is it?

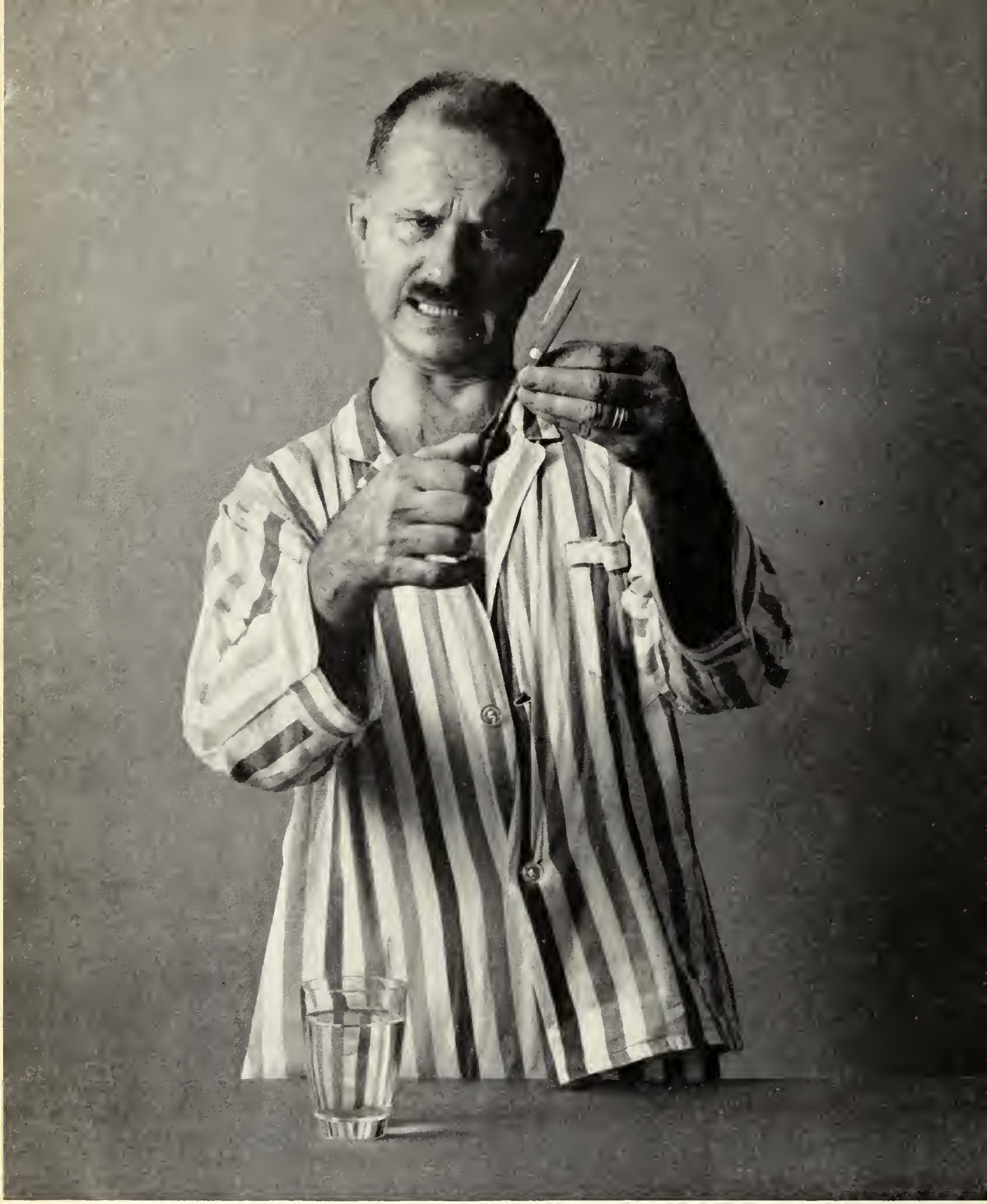
One big project for all to work on is to get programs put on in your junior and senior high schools telling about the many careers available under the title of Health Careers. There are over two hundred such careers and none of them are filled. We need many more trained people to fill these jobs. Our job is to interest young people in these Health careers.

It is our duty to keep up with the news and know what is going on. Don't stop with just the newspapers, radio and television. Learn about the things the AMA is doing and supporting which includes our husbands.—Read J.A.M.A. and *Connecticut Medicine.*

All the doctors wives should join their auxiliary so that they can help with these many projects.

Semi-Annual Meeting
November 14, 1967

The Woman's Auxiliary to the Connecticut State Medical Society will hold their semi-annual meeting on November 14, 1967 at the Carriage Drive, Whitney Ave., Hamden, Conn. This will be a luncheon. The speaker is Professor Humphrey and his topic is "Sex Education—Who, What, Where and Why." Everyone should try to be there.



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In Memoriam

Clifford, Martha L. — Hartford, University of Colorado School of Medicine, 1933. Dr. Clifford had been associated with the Connecticut State Department of Health for 31 years. She was director of the Community Health Division, which involved the supervision and leadership of five of the department's sections: Crippled Children, Maternal Health, Child Health, Nutrition and Public Health Nursing. Dr. Clifford's special field of interest was child health and infant and maternal care. Among the programs in which she had been involved were: adoption of the sanitary code regulations for child day care centers; expansion of dental health clinics; reorganization of children clinics; development of a rheumatic fever and heart disease program in New Haven; establishment of a hearing testing program for pre-school children; licensing of maternity hospitals and the Emergency Medical and Infant Care Program of World War II. She was a member of the Hartford County Medical Association, the Connecticut State Medical Society, the American Medical Association, the American Academy of Pediatrics, the American Association of Public Health Physicians, the American Association of Teachers of Preventive Medicine, and the American Public Health Association. Dr. Clifford died October 1, at the age of 58.

Lowell, W. Holbrook—Hartford, Harvard Medical College, 1937. Dr. Lowell was a practicing physician in the Hartford area for many years. During World War II, he served with the U. S. Army Air Force in Burma. Dr. Lowell was active in Hartford Hospital's Department of Medicine and Hospital Affairs in teaching and consulting services. He was also chief of medical services at McCook Memorial Hospital. He was a member of the Hartford County Medical Association, the Connecticut State Medical Society, and the American Medical Association. He was also chairman of the advisory committee to the State Board of Examiners for Nursing from 1963 to 1965. Dr. Lowell died August 26, at the age of 58.

Rowley, John C.—West Hartford, Harvard Medical School, 1906. Dr. Rowley was a general practitioner in the Hartford area for over 50 years. During World War I, he was a captain in the U.S. Army Medical Corps. He was assistant visiting pathologist at Hartford Hospital for six years and visiting pathologist for eight years. He was also the hospital's assistant visiting physician for seventeen years. He served as chief of staff at Hartford Hospital and was also a consultant to the Institute of Living. He was associated with the Public Welfare Board, the Board of Education, the Connecticut Medical Examing Board, the Visiting Nurses Association, the Hartford Tuberculosis and Public Health Association, and the Connecticut Children's Aid Association. He was a member of the Hartford Medical Society, the Hartford County Medical Association, the Connecticut State Medical Society, and the American Medical Association. He was a Fellow of the American College of Physicians. Dr. Rowley died September 9, at the age of 88.

Schuyler, Samuel A. — Hartford, University of London Medical School, England, 1939. Dr. Schuyler served as a hospital consultant in physical medicine and rehabilitation to the New Britain General Hospital, the Hartford Hospital, and the Connecticut Valley Hospital. He was a member of the Hartford County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Schuyler died September 24, at the age of 59.

BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Insurance For The Doctor. Edited by Harvey Sarner, LL.B. and Herbert C. Lassiter, LL.B. W. B. Saunders Company, Philadelphia and London, 1967. 193 pp. $9.00.

Diabetes Mellitus: Diagnosis And Treatment, Volume II. Edited by George J. Hamwi, M.D. and T. S. Danowski, M.D. American Diabetes Association, Inc., New York, 1967. 250 pp. $2.50.

Jared Eliot, Minister, Doctor, Scientist, And His Connecticut. Edited by Herbert Thoms, M.D. The Shoe String Press, Inc., 1967. 156 pp. $6.00.

NEW BOOKS IN REVIEW

CLINICAL JUDGMENT. Edited by Alvan R. Feinstein, M.D. The Williams and Wilkins Company, Baltimore, 1967. 414 pp. $9.50.

Reviewed by: LOUIS H. NAHUM

What is wrong with clinical medicine? Why have clinical scientists turned to animals and test-tubes for research instead of the patient at the bedside? Why has prognosis lagged and therapeutic evaluation been so difficult? Why do we still think of clinical medicine as an "art" and making a prognosis only a successful effort after years of experience which alone seems to make "clinical judgment" possible?

In this book we are given a guided tour of bedside practice, of clinical researchers, of the present inadequacies of prognosis and evaluation of therapy; of the stuffiness and sterility of most C.P.C.'s and of the failure of clinical medicine to prepare itself for the computer age. Professor Feinstein has taken up the cudgels to make clinical medicine into a science. It is his thesis that for a more precise evaluation of prognosis and treatment we need a new vocabulary which can explicitly state the nature of the symptom, the varied elements in physical signs. Then clinical medicine, which is now practiced as an art can come to be practiced as a science but it will require more precise clinical observation, more logic. The clinical data must be better enumerated and analyzed in the same way as other data are analyzed that are obtained in a laboratory experiment.

When a clinician sees a patient with myocardial infarction how does he recognize and record presence or absence of intractable pain, its location, radiation? How does he evaluate degree of sweating, shock, dyspnea, cyanosis, arrhythmias and other clinical manifestations? And yet it is with these nuances that we make choices as to therapy, when we treat, when we wait, when we use drugs or only words. Without correct clarification of the many variables involved, we cannot designate how we use them and our therapeutic reasoning becomes a non-reproducible procedure by others. This is a man's "clinical judgment."

We need then to deliberately arrange, deliberately to correlate the data so that a clinician can analyze their meaning in terms of prognosis and results of treatment. If we could do this we could begin to think about the data clearly, read or write about them formally. Professor Feinstein shows us how to construct a system of classification, a vocabulary for classifying personal features of the patient and for classifying agents of treatment.

The construction of such a clinical taxonomy is the first procedure of the therapy suggested in this book. Reasoning used to establish a diagnosis is first undertaken. The detection of clinical stage of an illness, clusters of symptoms and signs, their sequence and duration are features of human illness constantly observed by clinicians but have not received specific names and categories. The reason for this is probably the complexity of the problem. Although a diagnosis can have one designation, clinical distinction may require many different designations. The author mentions five types each with many variations all of which need to be contemplated simultaneously.

To enable formation of the classification and management of the complex data involved in clinical classification, we are shown how to use the new mathematics, symbolic logic, set theory and Boolean algebra. To aid their imperfect memories, clinicians can use the technologic device where factual capacity is vast and recall total—the digital computer a subject excellently portrayed in Chapter 10.

There is an excellent chapter on clinical indexes and importance of making them available for reasoning in evaluating therapeutic accomplishment. How do we now evaluate such findings as digitalis toxicity, antibiotic sensitivity, insulin shock etc.? If indexes do exist are there specific provisions for clinical effects? The clinical effects used in indexes are appropriately and reproducibly defined. We then have a devastating critic of reporting therapeutic accomplishment by means of judgmental or interpretive terms for which no criteria are given. There is a need for distinction between evidence and inference between index and interpretation between criteria and conclusion.

We are now approaching a solution to the need for specific clinical indexes. We have them in therapy for a number of diseases outlined. We have graduation criteria for citing quantity, severity and degree of a manifestation, for example dyspnea grade 1—3, angina grade 1-4, neurologic reflexes 0—4, loudness of a murmur 0—6. Transition criteria: better or worse, larger or smaller, aggregate criteria, a cluster of designations, improved, deteriorated, excellent. In short the clinician must observe attributes and establish criteria for classification.

We all know that clinicians have depreciated the scientific potential contained in clinical skills. They have been overawed by precision and standardization of laboratory technology. Professor Feinstein makes clear that in clinical investigation, if properly pursued, the scientist requires the same objectivity, precision and standardization as the laboratory scientist does. The only difference is that clinical science is more complex, has more variables to bring together.

In the prologue we have a fine autobiographical revelation of how Professor Feinstein grappled with the problems of clinical prognosis and treatment, how to systematize and make them into science, how the idea came to him in a flash one night at 1:00 A.M. while wandering in the streets of New Haven, and how one-half hour later he had classified the factors in prognosis of rheumatic fever and the extension of the principle to prognosis in cancer.

If this book was simply a work by a well disciplined mind, with exceptional talent for clear thinking and logical organization, enabled to extract, the essential fault that was responsible for the impasse that clinical medicine has reached, it would be an acute intellectual exercise but little more. But there is something more. What is this something more? It consists of two elements. First it shows how clinical medicine can be rehabilitated into a respectable science which should attract clinicians into expanding our grasp of prognosis and our ability to appraise the consequences of our therapy. The second is the establishment of a vocabulary and classification of symptoms and signs which on the one hand will make

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References: 1. Batterman, R. C., and Grossman, A. J.: Fed. Proc. *14*:316, 1955. 2. Goodman, L. S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 3, New York, The Macmillan Company, 1965, p. 331. 3. Roth, J. L. A., *et al.*: Gastroenterology *44*:146, 1963. 4. Conney, A. H., and Burns, J. J.: J. Pharmacol. Exp. Ther. *128*:340, 1960. 5. Settel, E.: Clin. Med. *6*:1373, 1959. 6. Berman, H. H., *et al.*: Dis. Nerv. Syst. *25*:430, 1964. 7. Darienzo, C.: Ibid., *27*:189, 1966.

*U. S. PATENT NO. 2,895,877

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the recorded data reproducible and on the other make it possible to utilize the memory of the computer, in assisting the bedside clinician to make better prognosis and carry out more reliable objective evaluations of our treatment. The concepts, explanations, intellectual methods to study human reactions to illness are clarified in this book.

The book is beautifully written in classic prose. It is aphoristic in style. It will be an inspiration in the pursuit of scientific methodology to students, clinical investigators and those aspiring to be good clinicians. With the systematic method worked out by Professor Feinstein, he and others to use it must further enrich clinical medicine converting it into a growing science, and a humanistic one. From now on clinical medicine will never be the same again. Clinical judgment has been placed on a scientific foundation.

THE HANDBOOK OF PRESCRIPTION DRUGS: Richard Burack, M.D. (Official Names, Prices and Sources for Patient and Doctor) Pantheon Books, Div. of Random House, New York; Paperback $1.95.

Reviewed by: PAUL H. LAVIETES

This handbook seems to me a must for physicians. While interesting and valuable for both patient and doctor, the appeal to the patient is not one which should offend most doctors. Nor is it unduly harsh on the drug companies. It presents a fine, brief, factual, and critical summary of the Kefauver hearings. It emphasizes that the doctors' primary responsibility is to the patient and that the company's efforts are not always in that direction, particularly in the areas of education and pricing. It makes a convincing case for the use of generic preparations and gives useful information as to their availability. The handbook's "Prescription Drug List" contains much useful material.

For the layman the handbook explains a great deal about the reasons for overprescribing and overpricing, and gives considerable useful information about drug therapy. Certainly this is much better than the sensational information so often provided in the articles on drugs in the lay press. For the physician the book could well provide a very useful bridge between Goodman and Gilman and the demands of therapy in practice. Revisions will undoubtedly lead to constant improvement as there will undoubtedly be many useful comments from physician readers.

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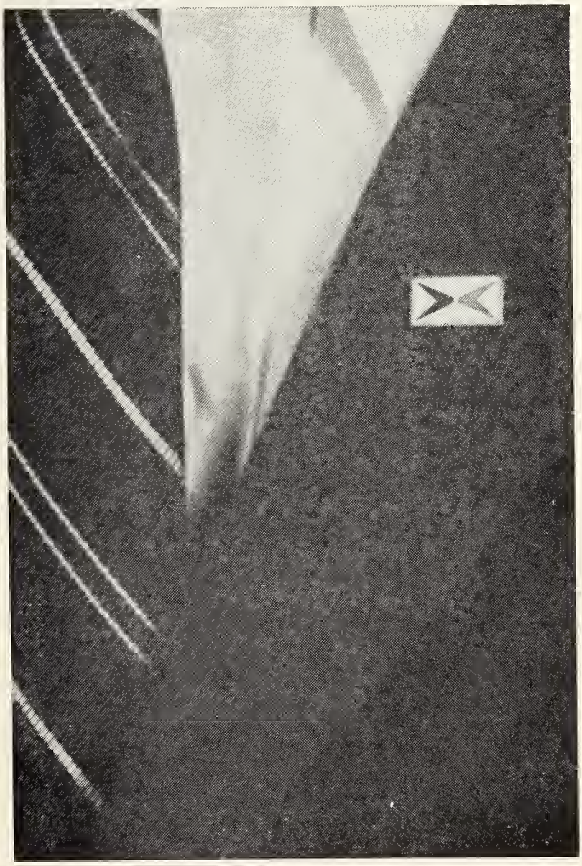

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SUMMARY OF COURSE

Lectures and demonstrations will be presented on basic theory and clinical application of radioisotopes and nuclear radiations. General concepts will be stressed with presently available applications cited as specific examples. This format is intended to provide a broad background for comprehension of both present and future developments in this field rather than a discussion limited to techniques presently in use.

One day of the course will be devoted to basic physics and radiobiological material. Three days will be devoted to general problems in tracer kinetics and diagnostic studies of specific organ systems. One day will be devoted to the use of radioisotopes and nuclear radiations in therapy.

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Hotel Claremont, Berkeley, Calif., Mr. E. P. Redfearn, Resident Manager, Single Rooms, $12.00, Twin-bedded rooms, $16.00.

NOTE: Bus transportation will be provided between the Claremont Hotel and the Lecture Hall. A book of lecture notes summarizing the material to be covered will be distributed on the first class meeting day.

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A POSTGRADUATE COURSE for PRACTICING PHYSICIANS

ADVANCES RELATING TO MANAGEMENT OF CARCINOMA OF THE RECTUM

Wednesday afternoons, November 22 & 29 and December 6, 1967

A series of three weekly afternoon sessions featuring lectures, workshop sessions, demonstrations, movies, case presentations, and question-answer periods. This series will review established concepts and present newer treatment methods for management of carcinoma of the rectum. The course is designed to cover practical aspects for the practicing physician.

November 22—Why And How We Can Do Better

1:30-2:00—Opening Remarks. Dr. Jack W. Cole, Ensign Professor and Chairman, Department of Surgery.

2:00-3:00—How to Establish the Diagnosis While the Disease Can be Cured. Dr. Joseph C. Cleveland, Instructor in Surgery and Cancer Coordinatior. Dr. Arthur R. Clemett, Associate Professor of Radiology.

3:00-3:30—Movie—Technique and Indications for Sigmoidoscopy.

3:30-4:00—Demonstration of Newer Instruments for Sigmoidoscopy.

4:00-4:30—Case Presentation, Discussion, Question-Answer Period.

November 29—After Biopsy, Then What?

1:30-2:00—Should All Patients with Cancer of the Rectum Receive Pre-Operative Supervoltage X-Ray Therapy? Dr. Morton M. Kligerman, Professor and Chairman, Department of Radiology.

2:00-2:15—Comment—Dr. Cleveland.

2:15-2:45—Pathology of Specimens Removed after Receiving Pre-Operative X-Ray Therapy—Dr. Romeo A. Vidone, Associate Professor of Pathology.

2:45-3:00—Question-Answer Period Concerning Pre-Operative X-Ray Therapy.

3:00-3:30—Must the Patient Have A Colostomy? What About Anterior Resection of A "Pull-through"? Dr. Cleveland.

3:30-4:15—Clinico-pathologic Review. Relation of Gross and Microscopic Pathology to Presentation and Prognosis. Dr. Vidone.

4:15-4:30—Question-Answer Period.

December 6—Other Problems

1:30-2:15—Role of Chemotherapy in Carcinoma of the Rectum. Dr. Joseph R. Bertino, Associate Professor of Pharmacology and Medicine.

2:15-3:00—Management of Late and Recurrent Cases. Dr. Cleveland.

3:00-4:00—What About Polyps? Dr. Cole and Dr. Vidone.

4:00-4:30—Workshop Session.

Program Director: Dr. Joseph C. Cleveland, Cancer Coordinator, Department of Surgery. Moderator: Dr. John T. Mallams, Emma Freeman Professor for Irradiation Research, University of Texas Southwestern Medical School, Dallas; currently Visiting Professor of Radiology, Yale University School of Medicine.

Time: 1:30 to 4:30 P.M. on three successive Wednesday afternoons, November 22 and 29 and December 6.

Place: Brady Auditorium, Yale-New Haven Medical Center (entrance at 310 Cedar Street).

Registration fee and tuition: $5.00 (for series of three conferences) Admission will be limited to physicians who have registered in advance. Enrollment cards will be given to registrants at the initial session. Interns and residents may register without charge.

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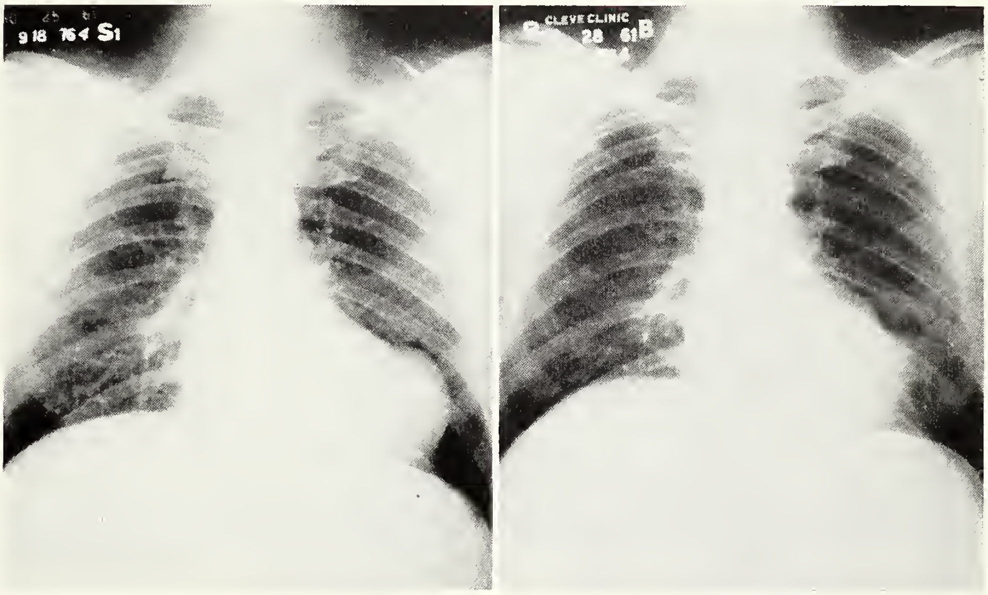
VENTRICULAR ANEURYSMS BEFORE AND AFTER SURGERY



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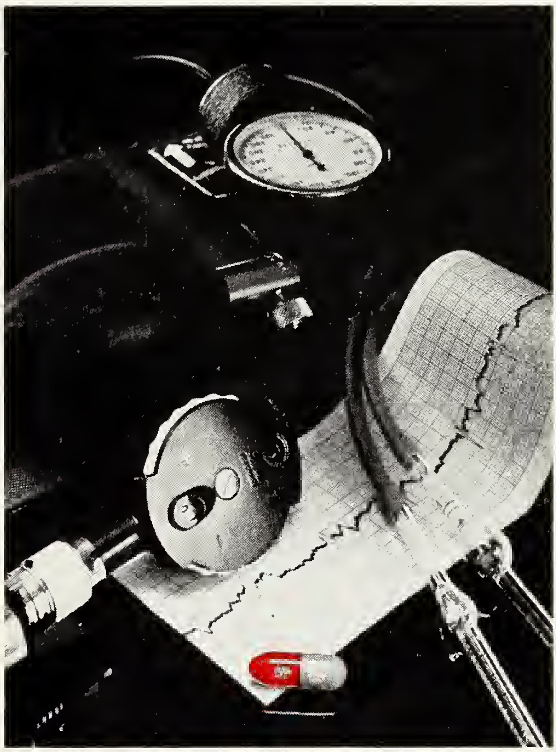

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Connecticut Medicine

editorials

Alcohol And Traffic Deaths

Motor vehicle deaths in 1958 were 36,981, in 1966 they were 52,500. In most of the cases there is a marked crushing or deformation of the cars involved. This means high speed crashes and this is where "speed kills" is derived. Why were these high speed cars so ill controlled that a fatal or very serious injury was the result? To be sure, the brakes may have been defective, the road slippery and poorly designed, the visibility poor. However, one very important reason is that well over half of all fatally injured drivers had been drinking. Among drivers found responsible for the fatal crash, two-thirds had been drinking and in one car fatal crashes seven out of ten had been drinking.[1] And so the question arises, what kind of drinking? After all millions of people drink and drive and are still alive.

We gain a glimpse of the reason from McCarroll and Haddon's[2] study of eighty-three drivers killed in one car crashes. Only 3 per cent had blood alcohol levels below .05 per cent. Half had blood alcohol levels of .15 per cent or more at death. Clearly drinking drivers deemed responsible for fatal accidents most often have the higher blood levels. This fact was recognized as far back as 1926 in Norway[3] where everyone who violates the drinking law goes to jail. Suspension of fines and jail sentences, the curse of the American road is not known in Norway. Sweden joined Norway in 1957 in making .05 per cent blood alcohol level as the limit for drivers.

We must remember that normal civilized leisurely consumption of alcoholic beverages in the course of a good dinner will almost never produce a blood alcohol level above .05 per cent. Even below this level impaired driving may result since 20 per cent of drivers with this level will be grossly impaired. But as a practical limit which will not interfere with good living, the .05 per cent limit will prevent abnormal driving for the most part. This was the conclusion of a superbly conducted controlled test and can not be exaggerated.[4]

With the repeal of prohibition in 1933, motor vehicle deaths in the United States increased spectacularly from 31,363 in 1933 to 39,643 in 1937[5]. Alarmed by this rapidly developing trend the AMA appointed a committee to study the problem of motor vehicle accidents and its attention was almost entirely devoted to the matter of the drinking drivers. The committee advocated that persons with a concentration of less than .05 per cent should not be prosecuted for driving while under the influence of alcoholic liquor, that persons with concentration above .15 per cent show definite loss of clearness of intellect and control of themselves. Between .05 per cent and .15 per cent a great many persons definitely will be under the influence. It would seem that the logical thing is to place levels at which almost no-one is impaired, the very point accepted in Norway forty years ago. To place the ceiling level at .15 per cent was a clear mandate for the chronic alcoholic to drive upon our public highways and place innocent people in jeopardy. Unfortunately because of the AMA mandate the courts set 0.165 level dividing drunk and sober! Only a higher figure could be further from the truth.

The result of this all too tolerant approach has been mentioned above, that half of all fatally injured drivers had been drinking; among drivers found to be responsible for fatal accidents, two-thirds had been drinking and in the one car fatal crashes seven out of ten had been drinking. The result was that the figures accepted above was reversed in 1958 and it was stated that blood alcohol concentrations of .05 per cent will definitely impair the driving ability of some individuals and as blood alcohol concentration increases a progressively higher proportion of such individuals are so affected until at blood alcohol concentrations of .10 per cent all individuals are definitely impaired.

Two obvious inferences from the data that have accumulated are, first that the problem drinker, the chronic alcoholic played an inordinate role in traffic accidents, and the other is, that it is urgent that we approach the problem of the alcoholic by treatment not punishment. It is estimated that there are be-

THE COVER

Figure 3. A Ventricular aneurysm in a 53-year-old diabetic man five days after acute anterior infarction. B, Roentgen appearance of the same patient two months after aneurysmectomy was performed because of congestive heart failure.

tween five and six million chronic alcoholics in this country and that about 80 per cent of them drive automobiles.

Drivers under age twenty-four have the highest death role of any age group[6] and a large proportion of them are heavy drinkers. When influenced mentally by alcohol he does not realize how fast he is driving and is in no physical condition to control a car driven at high speed. A large proportion of them are heavy drinkers although they are not yet chronic alcoholics but they have a drinking problem.

Even though the cure of the chronic alcoholic is difficult and time consuming and subject to relapse, we must make a first step in this direction. The first step in a rational approach is to consider the alcoholic and psychiatric aspects of traffic safety by the establishment of a psychiatric clinic in conjunction with both the criminal and traffic divisions of all the lower courts in the nation. Clinics in Chicago, Detroit, New York and Baltimore are prototypes and examples in this field. In place of the "revolving door" policy operating in most areas, in these cities a repetitive offender or a questionable first offender is referred to the clinic for evaluation before sentencing. It is amazing what an assortment of abnormal people have been provided with valid drivers licenses [7,8].

When an investigation of his background by the psychiatric clinic reveals that a given driver, even in his first offense, is a problem drinker or a chronic alcoholic it is futile to fine him or send him to jail or to suspend him and then give him another chance. He must be referred to a specialized treatment center and while here every service should be provided to help rehabilitate him. This includes psychiatric evaluation and treatment, alcoholics anonymous and Pastoral counselling. It is essential that he be kept off the road until there is reasonable assurance that he can drive normally.

The report of Selzer and Weiss[9] has great significance. Many of the alcoholic drivers had a long history of serious psychopathology. They were paranoid, violent, depressed, suicidal. Some had just been released from a state mental hospital after undergoing treatment for habitual alcoholism.

Campbell[5] calls attention to three recent events of great importance to the chronic alcoholic. In the Easter vs. District of Columbia and in the Driver vs. Hinant (North Carolina decisions[10,11]. two U.S. Court of Appeals have held that a chronic alcoholic may not be convicted for being intoxicated in public. Judge Samuel M. Kirbens writes[12] "Rehabilitation of the alcoholic must truly become an inter-disciplinary enterprise. The disciplines of law, medicine, penology, psychiatry, welfare, and religion all have a role to play in devising civil procedures to replace outmoded criminal sanctions."

This new scientific approach to the problem may be seen further in the announcement on October 1966 that a National Center for Prevention and Control of Alcoholism has been created at the NIMH at Bethesda, Maryland. Also, the National Traffic and Motor Vehicle Safety Act of 1966 and the Highway Safety Act of 1966 which will bring influence to bear upon state highway safety programs.[5] If we accept the Norway limit of .05 per cent blood alcohol levels and work to rehabilitate our alcoholics we will avoid not merely the death of the alcoholic himself on the highway but the innocent driver with whom he collides.

L.H.N.

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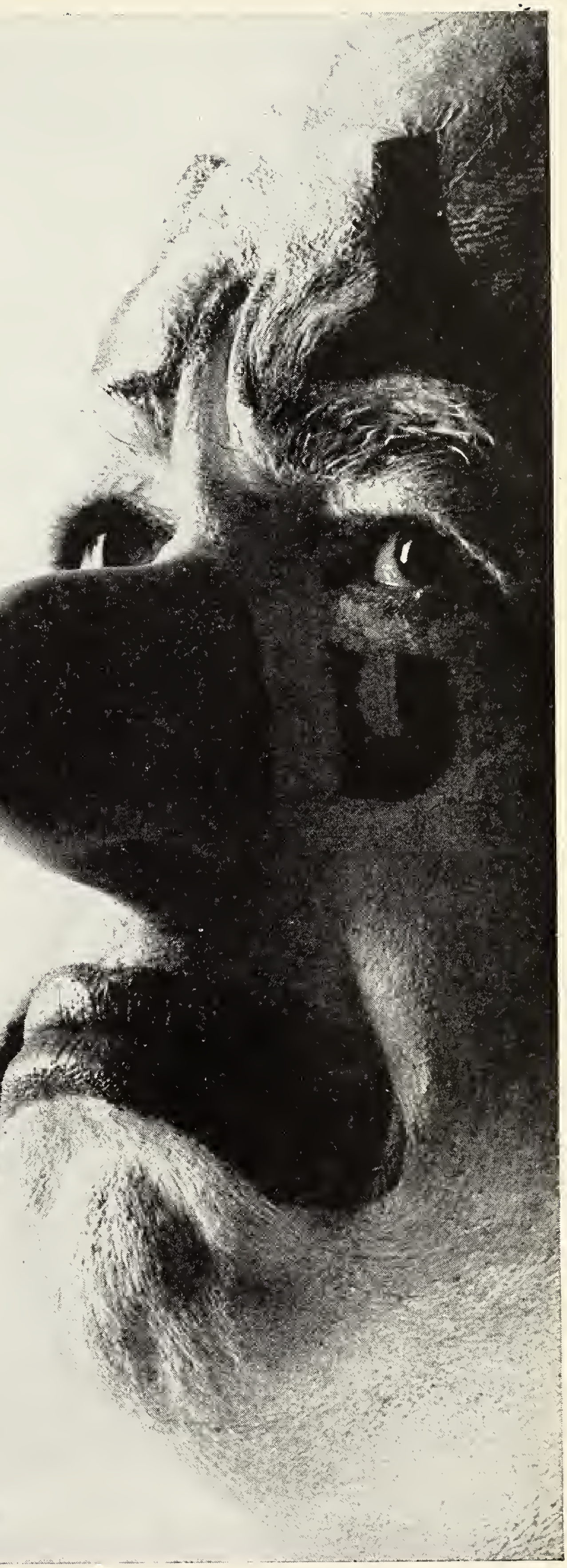

The Present Status of Hodgkin's Disease

Hodgkin's disease is responsible for one out of every hundred deaths due to cancer in this country. It is found the world over and seems unrelated to status or occupation. It is twice as common in men as in women with a peak frequency in the third decade although it has been reported in very young children. When it begins, its symptoms are often suggestive of inflammation or an infectious process but at its end it most closely resembles a malignancy. In the past many organisms have been considered etiologic agents but now interest centers on the possible role of the immune mechanism in pathogenesis and on viruses in etiology.

An important recent development in Hodgkin's disease is the realization of the significance of staging in the prognosis and treatment. Because of improved diagnostic aids in the laboratory and radiology the extent of the disease can be delineated much more precisely. The stage of the disease is probably the most important factor in indicating the type of therapy to be employed as well as in estimating the prognosis. The stages are defined in I—IV categories according to the classification that was adopted at the 1965 conference mentioned by Perry. Stage I is when the disease is localized in one anatomical region, most commonly an enlarged group of nodes on one side of the neck. Stage II is when the disease is limited to two regions. In Stage III disease is on both sides of the diaphragm but limited to involvement of nodes, spleen and Waldeyer's ring. Stage IV is involvement of bone marrow, parenchyma of lung, liver and bone.

Treatment is likely to be most successful when the disease is first diagnosed and hopefully localized to a few lymph nodes. In such patients Johnson reports an excellent response to radiation therapy especially if there is absence of constitutional symptoms. There is now historical evidence that many of these patients can have a normal life expectancy. Even in patients with constitutional symptoms or more widespread disease or both, there is observed complete disappearance of tumor and symptoms after radiotherapy and a majority of these patients have remained clinically free of Hodgkin's disease after completion of treatment. By using the available information on the radiation dosage required to eradicate Hodgkin's disease locally, there is available the opportunity to apply a rationally designed and potentially curative treatment regimen to the majority of new patients who are diagnosed early. For this reason radiotherapy is used in stage I and II in which drugs are not to be used.

We must remember that drugs affect not only tumor cells but almost always normal tissues as well. However, Hodgkin's is a responsive tumor and with proper drug therapy one can expect excellent clinical control of the disease for relatively long periods of time even years. Besides this is the fact that several agents are all effective in shrinking tumor masses in patients with Hodgkin's disease. The agents are not cross resistant and therefore may be used singly or in combination simultaneously. The four clinically proven drugs of value are nitrogen mustard, chlorambucil, cyclophosphamide and vinblastine. In addition there is benzmethyzine HCl, and prednisone each effective from 30—100 per cent of cases.

When these drugs are properly used one can expect relatively long control of the disease. The problem still remains concerning the optimum use of these compounds. There are available three measurements of response that one must follow in the use of these drugs. One is estimation of the drug's ability to induce a remission. Another is the duration of the remission induced. Finally is the effect of the drug on survival. Dr. Carbone points out that from his experience vinblastine is the first drug of choice and can induce a remission in 80 per cent of patients whether treated intermittently or continuously.

The search for specific etiologic agents as well as specific curative therapy is being actively pursued by many laboratories. However, it is well to remember that present day chemotherapy can control the symptoms and signs of the disease in most patients. Single agent chemotherapy destroys large numbers of tumor cells. Combination chemotherapy probably destroys more. Therefore, survival of patients should be improved by proper manipulation of the available therapeutic drugs. Survival of patients can be prolonged, complete eradication of tumor cells can be achieved in some patients and thus there is now good reason for a more optimistic outlook in Hodgkin's disease.

In Hodgkin's disease there appears to be a dissociation between antibody formation and delayed hypersensitivity. There is definitely an immunologic defect. If we could correct it would the patient be improved either by regression of the lymphoma or by enhanced resistance to infection which is such a prominent feature in the late stages of Hodgkin's disease. It seems, however, that the

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degree of immunologic impairment is related to the anotomic extent of the disease and this would suggest that the impairment is secondary to the disease and not a pre-existent etiologic event.

There is as Dr. Haynes points out a striking relationship between immunologic reactivity and the peripheral lymphocyte count. There is also a lymphocytic depletion in biopsied lymph nodes. Finally there is evidence that the lymphocyte in the peripheral blood of Hodgkin's disease patients do not perform normally in vitro. If the depression of antibody formation were due to insufficient numbers of functional lymphocytes what would happen if we gave normal lymphocytes by infusion in such patients? Up to the present time this method has proved unsuccessful. The evidence up to now is that the immunologic impairment is a consequence of the stage of Hodgkin's disease and is not an antecedent factor. For the present we must rely on the production of a remission of the disease by radiology and chemotherapy in order to improve the immune competence. If there is an immunologic defect in Hodgkin's disease we have an explanation for the frequency of various infections that afflict patients in the later stages of the disease.

L.H.N.

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Experiments In Medical Education: The Method Of Self-Assessment

All physicians who graduate from a medical school spend the rest of their lives in the pursuit of medical competence. What must they do about continuing this education every day of their lives? The half-life of medical knowledge is now six to seven years. This means we must learn new knowledge, a new vocabulary and its usage. We try to do this through medical meetings, postgraduate courses and discussion with other physicians. There will emerge many new methods of learning such as programmed instruction,[1] various kinds of self evaluation, films, tapes, computers. But how do you come to be motivated. First the physician needs to know he is falling behind. He must know

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whether he is up to date or not without fear of losing status or privileges.

The American College of Physicians began to grapple with this problem and appointed an ad hoc committee which viewed all the various efforts made in relation to continuing education.[2] Most of these were very good but there seemed to be missing from all these programs one common denominator. This was the factor that no one including himself knew what the doctor did not know that he should know. In other words the physician needed to evaluate himself, his own knowledge. It was assumed by the Committee that physicians do want to learn and increase in excellence; that they would like to know their deficiences provided no one else knew them.

After many hours of discussion it was decided by the Committee that they would propose some form of voluntary self-evaluation of the members. The plan was essentially as follows: members would volunteer to take self appraisal of their medical knowledge in internal medicine; this would be taken at their convenience with or without help, the answers would be graded by a computer and the results would be sent by confidential mail back to the member; the computer would print out references for these questions which were answered correctly or incorrectly and the name and series would be erased.

The idea was simply to allow the members who wish, to have a self-assessment of their medical knowledge in various areas, neurology, heart and vascular, gastroenterology, pulmonary, infectious disease and allergy, kidney, hematology, rheumatology, endocrinology and metabolism. It is anticipated that the self-assessment study will take about eight hours to complete. The College, of course, is most anxious to know if this and other types of plans for continuing education are needed and wanted by the members. They want the members to find out what was new in the specific fields which might be applied in the practice of medicine.

Of course, the ultimate goal of all continuing education is to influence the physician's patterns of practice and elevate his standards. Self-assessment is only worthwhile if the physician is motivated to continue to improve his knowledge. Although large numbers of postgraduate courses, 1,641 in the year 1965-1966 have been and are being given there are many faults with the current offerings in postgraduate education. Often they are archaic, inappropriate and ineffective and rarely is the registrant given an opportunity to

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participate actively. The lecture method which is being abandoned in undergraduate education still remains the backbone of postgraduate programs, even though we know that retention of materials from lectures is poor. The subject matter and presentation may not be pertinent to the practicing physicians needs or interests. The curriculum is usually fragmentary and not systematically planned.

The deterrents to continuing education of the physician are now known. No one takes care of his patients while he is away. Courses are held at unsuitable times. Cost in money and time away from practice is prohibitive. There is a multiplicity of other meetings. The subject matter is not suited to the physician's needs. There is a lack of courses in the physician's area. There is previous unsatisfactory experience with poor courses. There is lack of information about courses. In spite of these handicaps the number of courses has increased 50 per cent and registrants threefold, so avid is the physician to improve his standards of practice.

There remains, however, two paramount questions we must ask ourselves. Are the postgraduate programs reaching the physician who most needs help? Are we providing educational opportunities which will alter the physician's way of practice and elevate his standards? There are many physicians who have never seriously been involved in any form of continuing education, no postgraduate courses, irregular attendance at hospital staff meetings, unopened medical journals and attendance at medical meetings especially for their social functions. There is no reliable data on how many such physicians there are.

The other question is even more thorny: are our traditional efforts in postgraduate medical education achieving their goal with those who do participate? Do they actually affect changes in the physician's pattern of practice and elevate his standards; are the physician's basic attitudes improved? Efforts to evaluate the effectiveness of postgraduate courses have not been very fruitful and again one can only guess. The method of self-assessment suggested above could in time uncover answers to these questions.

L.H.N.

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The Median Eminence Gland: A Neuroendocrine Transducer

We have known for a long time that the anterior pituitary is affected by the brain. There are case reports of pituitary failure following hypothalamic disease. When sarcoid damages the stalk of the pituitary it produces the "pituitary denervation syndrome" much as section of the stalk does. In this case secretion of tropic hormones of the pituitary is inhibited. We also know that in certain animals there is neural control of gonadal function. Some ovulate only after copulation. Some have endogenous neural rhythms for ovulation.

The part of the hypothalamus which is now known to control pituitary function is the median eminence gland. This structure forms the central portion of the base of the hypothalamus. It has been modified so that substances secreted by nerve endings in this region can be transmitted by way of blood vessels to the anterior pituitary through its stalk. This structure is quite analogous to the posterior pituitary (neural lobe). The hypothalamus synthesizes most of the anti-diuretic hormone (ADH) which is conducted by axonal flow through the axons to accumulate in nerve endings in the neural lobe. After an appropriate physiologic stimulus to release the ADH, the propagated action potential triggers the release of ADH, preformed and waiting, stored in the nerve endings of the neural lobe.

A similar process occurs in the median eminence which is innervated by the endings of very small fibers that are located around the base of the hypothalamus. There nerves end in relation to the perivascular capillary spaces and the blood from these capillaries is delivered finally to the anterior lobe by the hypophyseal portal circulation. The arterial blood which perfuses the median eminence capillaries is enriched by these neurohumors. Thus the median eminence gland is the critical transfer zone that seems to be important in neural pituitary control.

Visualization of this system in animals has been achieved by perfusion with India ink. The electron microscope reveals that the median eminence gland is made up of a mass of packed nerve endings, capillaries and perivascular spaces. The neurohumoral material is in nerve vesicles in the clubbed nerve endings. As the vesicles empty, the preformed neurohumors diffuse through the plasma membranes, perivascular spaces, capillary basement membrane, capillary endothelial wall, and then enter the portal vessel blood stream.

There are many classic experiments that support the view that this region of the brain is uniquely capable of regulating anterior pituitary functions. Some are even taken from transplantation experiments in which only when the median eminence is placed in proper relation to the anterior pituitary, will pituitary function develop normally.

If the median eminence is indeed a neuroendocrine organ for regulation of anterior pituitary function, then it should be possible to cause defects in pituitary function by means of destructive lesions in the median eminence gland. By stimulating this region electrically it should be possible to cause secretion by anterior pituitary. Finally it ought to be possible to isolate the neurohumoral transmitters which are capable of altering pituitary function. All of these experimental models have been employed and found confirmatory of the role of the median eminence gland in controlling anterior pituitary function.

When Glick and his associates developed an immunochemical assay for estimating growth hormone in the plasma, a tool was made available to study one of the anterior pituitary hormones. This was especially felicitous when it was shown that hypoglycemia induced by insulin causes growth hormone discharge and thus it was possible to investigate what structure is responsible. Reichlin[2] by elegant experiments producing lesions in various areas of the nervous system found that only lesions in the median eminence prevented growth hormone liberation. In short the growth hormone discharge in response to hypoglycemia depends upon the integrity of the median eminence and the neural mechanism is operative both in laboratory animals and man. In addition to liberating growth hormone, a number of other neuroendocrine reactions are also hypoglycemic responsive. There is reflex ACTH, and epinephrine release also.[3-6]

If the median eminence is a gland it ought to be possible to find its hormone and to show that these hormones affect the anterior pituitary. For example the growth hormone releasing factor probably is secreted into the hypophyseal portal vein blood. It has been extracted from the median eminence after electrical stimulation. Other releasing factors isolated are the corticotrophin releasing factor which causes discharge of ACTH. Thyroid stimulating hormone releasing factor has been identified and found effective in very high dilution. Similarly luteinizing releasing factor has now also been identified.

All of these releasing factors described above stimulate the anterior pituitary. In their absence pituitary function is decreased. The only exception was found to be prolactin. This hormone seems to be secreted in increased amounts when the pituitary is separated from the median eminence. In other words the median eminence is a restraining influence upon prolactin secretion and when this restraint is removed only then is prolactin formed.

The median eminence gland then may be viewed as a neuroendocrine organ the specific function of which is control of the anterior pituitary gland. The amount of control exerted is somewhat variable from one tropic system to another. For some systems as for the growth hormone, there is a reasonable amount of autonomy. For thyroid stimulating hormone there is somewhat less autonomy and the gonadotropic hormone secretion is almost totally dependent on hypothalamic influences.

It is interesting to speculate how these secreting factors arose phylogenetically. There is a polypeptide in hypothalamic extracts that acts as a salivary gland secretogogue in the rat. The anterior pituitary gland embryologically is derived from tissues of the foregut closely adjacent to the primitive diencephalon. Perhaps the primitive median eminence at one time released secretogogues that influenced the primordial pituitary gland. When it became a ductless gland perhaps these secretogogues then evolved into the pituitary releasing factors.

Another source of speculation is whether each type of pituitary cell is a cell unto itself only having one function and that there are specific releasing factors for each cell or as in the case of prolactin, specific inhibiting factors for each cell. Or perhaps whether the stimulating factor for one hormone is inhibitory for another. Thus if TSH release is stimulated with thyrotropin releasing factor, it at the same time inhibits ACTH release by the same cell.

As far as the median eminence is concerned, it is hypophysiotropic—that is this part of the brain is specialized to secrete material that can cause differentiation and increased pituitary function.

L.H.N.

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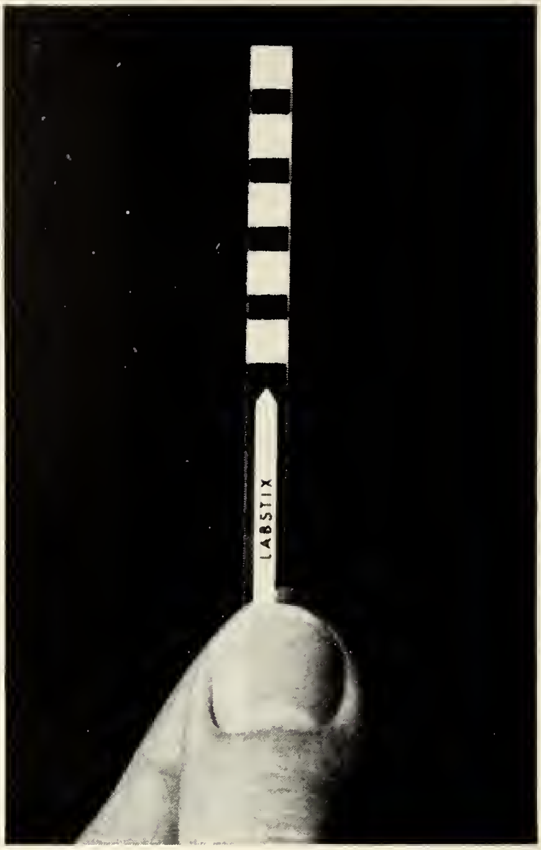
Pest Control By Biological Agents

Thousands of samples of food are examined by the F.D.A. each year to determine compliance with established pesticide tolerances on raw agricultural products. Residues of pesticide chemicals are found in about half of the samples and generally about three per cent of the samples contain residues in excess of or not authorized by legal tolerances.

At a joint meeting of the food and agricultural organization of the UN, WHO expert committee on food residues, acceptable daily intake of certain specified chemicals were proposed.[1] For DDT .01 mg. per kg. For lindane .0125 mg, per kg. For metathion .02 mg. per kg. For carbamyl .02 mg. per kg.

In view of these "acceptable tolerances" what is really being taken in by the American populace? Duggan[2] directs his attention to the average daily intake, calculated from the finding of all pesticide chemical residues in or on diet samples collected on forty-six days in twenty-five different cities during a 699 day period from June 1964 to April 1966. The sixteen to nineteen year old group was selected because they consume greater quantities and kinds of food than other population groups. The samples can be characterized as random. They came from retail stores in three different cities representing three geographic areas. The next year five geographic areas were covered.

The food samples were collected in the same way a customer selects his food in a retail store. Some food originated far from the place it was marketed. The total chlorinated pesticide residues taken in was .08–.12 mg. per day. The major source of chlorinated residues was found to be meat, fish, poultry. This combined with dairy products accounts for more than half the intake of chlorinated residues, while fruit, garden fruits, and grains each account for 10 per cent of total intake of this diet. DDT alone accounts for one-third total intake. Together with its analog dieldrin lindane, heptachlor, hepoxide, account for



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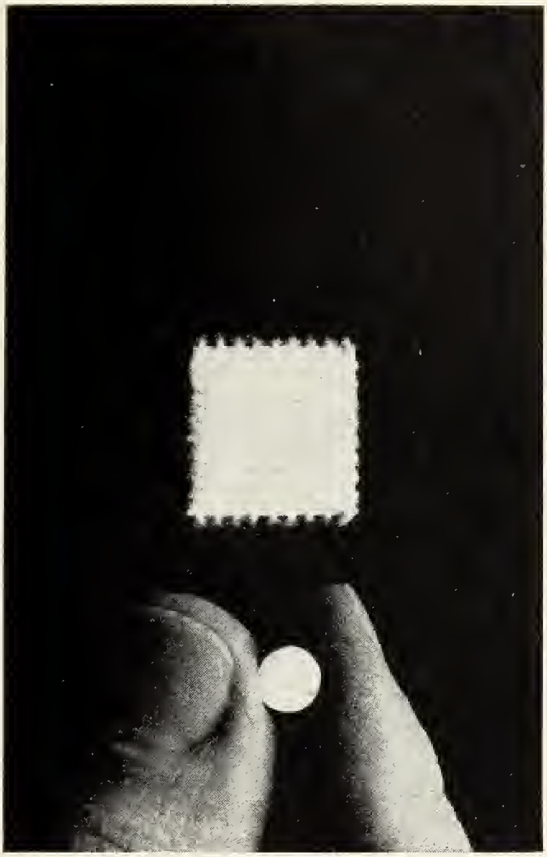

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85 per cent of total intake. The frequency and quantity of fourteen additional chlorinated pesticides were too low to be meaningful.

The findings of Duggan indicate that the actual intake of pesticide chemicals is much lower than the acceptable daily intake or potential consumption at the tolerance level. They are substantially below the limits set for acceptable daily intake by the WHO and UN committees and below the safe levels anticipated when legal tolerances are established on raw foods.

Although this conclusion is reassuring it cannot be said that pesticide residues in foods are not a matter for continued concern. Unpublished data obtained from objective samples of raw food examined to determine compliance with tolerance show that for each of the last three years almost half of the lots examined contained residues mostly below tolerance levels. However, over half of these lots contain more than one residue. Even though this investigation does not show a statistically valid difference there is nevertheless a definite increase in the daily intake of total chlorinated organic compounds. We must remember that even the acceptable tolerances are those considered safe based only on our present knowledge. And who is to say which individual may be more or less sensitive to these poisons and what their long term effects will turn out to be.

It is, therefore, comforting to know that conservationists interested in organic gardening and biological warfare against insects are developing techniques which may soon match the effectiveness of chemical poisons without endangering humans, pets or wildlife. The "secret weapons" of the conservationists are three types of insects: ladybugs, six inch grasshopper—like mantises and tiny wasp-like creatures called trichogamma. These insects thrive largely on leaf-eating aphids and a variety of other tree and shrub-killing insect pests and their eggs.

Early last June, Jaedicker and Norsgaard released 300,000 ladybugs and a variety of the mantis and trichogamma in an area beside the Hudson River in New York. Two months later they found their treated area matched completely the good results found in other areas where the Parks department had used poisonous chemical sprays.

If this preliminary experiment can be realized after two to three years of repeat trials, perhaps it may become possible to abandon poisonous pesticides in favor of a biological method that will

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L.H.N.

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The Microneuron

Altman has recently discovered that the great majority of a class of neurons in some important regions of the brain are found after, not before birth. Using a radio-tracer technique he demonstrated in cats, guinea pigs and rats that as many as 80–90 per cent of the neurons in three sections of the brain (hippocampal dentate gyrus, olfactory bulb and cerebellar cortex) form only after the animal is born. The number of these postnatal cells as well as their structural connections appear to be influenced directly by the environmental experience of the infant.

In all instances neurons formed after birth are of a type Altman calls microneurons. The cell bodies are relatively small in size and their axons short, making connections only within the same anatomical substructure. The macroneurons present in each substructure before birth have much larger axons and make connections with other even distant regions of the brain. These can be thought of as a genetically determined skeletal network which defines the input and output paths for the region. For example in the cerebellum, the large Purkinje cells are already present at birth and their axons connect this structure to the deep layers of the cerebellar nuclei and brain stem.

In anatomy texts we find associated with the Purkinje cells, three smaller types of neurons: basket cells, stellate cells and granule cells which we would now classify as microneurons. It was Cajal who suggested that these smaller neurons have only local output connections and serve as association elements providing connections between the microneuron cells, and that these associated connections become elaborated and enriched upon maturation.

Altman's view is that the development of practically all these cells is post-natal, and that this development is induced by the infant animal's attempt to engage in the type of behavioral activity that the region of the brain serves to modulate. The cerebellum, for example, serves to coordinate, adjust and smooth out movement. In the higher mammals, the awkward motion of the young infant indicates that at birth the regulatory influence of the cerebellum is mostly absent. It develops gradually over a period of time—twenty-one days in rats, twenty months in man.

With radio tracer techniques it has become possible to show that during this period layer upon layer of microneurons form in the cerebellum from a central pool of undifferentiated cells or neuroblasts and that the appearance of these new cells is correlated with the gradual refinement of motion in the infant. These microneurons are essential for normal movement in the mature animal. If their growth is inhibited by low dose X-ray, then the adult rat is ataxic and cannot coordinate his movements.

If rats are reared in an environment offering freedom of movement and play they show much greater proliferation of these microneurons, than rats whose activity have been restricted. Furthermore, animals that are handled also show more cells than those not handled. Atlman now has an experiment underway to compare the development of pairs of rats, one of which must learn to perform a visual discrimination to get food while the other experiences the same environment and feeding schedule but will not be required to master the discrimination task. It should reveal whether active learning promotes proliferation of micro neurons in special sections of the nervous system. At any rate information thus far supports the hypothesis that growth in population of micronurons occurs during infancy in response to feedback from the environment rather than merely as a genetically directed process that appears to take place in the post-natal period. This finding contradicts the common assumption that the ten billion neurons in man are all essentially present at birth and that post-natal development is confined to elaboration of connections within this existing neuronal network.

Nature seems to be able to program the demands of the environment into the morphological organization of the brain. The higher up one goes in the evolutionary tree in the mammal the greater the fraction of neurons in the brain are believed to be microneurons. The post-natal formation of these cells is thought to be of the greatest im-

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portance in man and continues for the most extended period of life. For example, proliferation of microneurons takes place in the human hippocampus as long as four years after birth.

Perhaps in man and other higher animals microneurons continue to form and elaborate at times very rapidly and then more slowly throughout life providing the associated connections in certain regions of the brain such as the cortex. As yet little has been observed about the formation of microneurons in the cortex since identification of microneurons with radioactive tracer techniques is less successful in this region than in more laminated structures such as the cerebellum.

The intimate connection of microneurons with the development of learned behavior in the few regions of the cortex so far studied has led Altman to raise the questions whether environmentally induced formation and elaboration of microneurons may not prove to be the physiological mechanism underlying long term memory. Can the mechanism of depression in infants separated from their mothers be due to inadequate environmental stimuli to the formation of microneurons?

We are beginning to learn of critical periods in behavioral development, critical periods in learning, critical periods in development of muscular coordination. The discovery of microneurons and their post-natal development as in response to the appropriate environmental stimulus, has opened a whole new field for the study of human development. Let's learn when and how to stimulate the formation of microneurons and thereby hasten the physical and intellectual development of the growing infant, child and adult.

L.H.N.

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Understanding The Stroke Syndrome

It is now well known that cerebral infarction and not intracerebral hemorrhage is the most common type of apoplectic disorder of the brain. Furthermore, the occlusive atherosclerotic disease responsible for the ischemic change is characteristically segmental and frequently localized to the extracranial vessels whereas the intracranial vessels may often be relatively free from disease. With early recognition of an accessible localized lesion being made possible by total angiography restoration of vessel flow has produced a remarkable salvage of potential stroke victims.

Recently Longheed[1] reported on 109 patients with extracranial internal carotid artery stenosis or complete occlusion in whom vascular reconstruction was attempted. Symptoms were arrested in 93 per cent of the patients with transient ischemic attacks and in 83 per cent of patients with strokes in evolution. These authors advise vascular reconstruction even in completed strokes if the patient is not drowsy and hemiplegic, not to restore function to an already infarcted brain, but to enhance collateral circulation and prevent the early occurrence of a second and probably fatal stroke. The uncertain results and the serious complications which can follow the treatment of this disease with anticoagulants has accentuated the value of surgical management.[2]

About 80 per cent of the patients with spontaneous hemorrhage into the cerebral or cerebellar hemispheres have signs of arterial hypertension. Various pathologic features have been described from microaneurysms, small vascular anomalies, to areas of subintimal dissection and medial degeneration in the perforating vessels. Most hemorrhages in the cerebral hemispheres arise from vessels in the external capsule or in relation to the internal capsule and may erupt explosively into the ventricular system. In addition to the local destruction the blood may spread down into the brain stem. If they are severe and destructive, these hemorrhages result in a high mortality and do not constitute a surgical problem.

If the hemorrhages arise from more laterally situated vessels in the region of the external capsule, they may also rupture into the ventricles and subarachnoid space, but they are more prone to split fiber tracts and present as a space occupying hematoma in the frontal, temporal and parietal regions. This type intracerebral hemorrhage produces little destruction of tissue but because of the asymmetric increase in intracranial bulk and the increase in intracranial pressure, may rapidly produce displacement or distortion of the brain stem. It is in these patients that carotid angiography can reveal the nature and location of the lesion and help identify a hemispheric mass. If the patient fails to maintain progressive improvement or shows signs of slow deterioration, an operation will limit and reduce disability. The surgical treatment is still controversial and there are champions of simple burr hole aspirations and also of formal craniotomies in all case.

In acute cerebellar hemorrhage there is headache, vomiting, vertigo and impairment of conjugate gaze. The pupils are markedly constricted and there is periodic respiration. There is no hemiparesis, aphasia or homonymous field defect. Ideally, localization should be confirmed by angiography and ventriculography. But if the patient is in poor neurological condition with failing vital function, he is a surgical emergency and should be operated upon immediately because delay may result in sudden death. As in patients with extradural hemorrhage, an area of the brain is involved in which the residual effects of the bleeding are minimal and if pressure can be reduced before the effects of brain stem compression become irreversible, excellent recovery may be expected to follow.

If the patient has a lesion in the nature of an intracranial aneurysm, the first indication of its presence may be onset of a subarachnoid hemorrhage although some aneurysms will present with neurologic deficits without hemorrhage. The treatment of the patient who has an intracranial aneurysm is conservative to provide optimum conditions for natural repair of the ruptured vessel, usually a period of six weeks rest, together with hypotensive therapy. However, patients treated conservatively have a mortality of 30 to 50 per cent and it has been demonstrated consistently that appropriate surgical treatment can reduce this figure.[3]

Early operative intervention for a ruptured intracranial aneurysm is indicated only when there is evidence of a large intracerebral hematoma. Once the patient has recovered from the initial insult operative treatment is not directed towards controlling the initial bleeding but is designed to prevent a recurrence of the hemorrhage. In this case obliteration of the sac is the treatment of choice but this is not always possible because important vessels may arise directly from the sac. In such patients reinforcement of the wall with muscle, fascia, gauze or plastic has had varying degrees of success.

Next to vascular hypertension and aneurysms the arteriovenous malformation is the most common cause of spontaneous intracerebral subarachnoid hemorrhage. The lesion is frequently cortical in location and the first indication of the presence of a hematoma may be bizarre. The case for surgical intervention is not so common and the attendant mortality and morbidity is much lower.

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However, if the lesion is in an accessible area, then resection is the treatment of choice. Successful removal is attended by a low operative mortality and morbidity and the patient is permanently freed from the possibility of recurrent hemorrhage and effects of mechanical compression of adjacent structures and this reduces the incidence of seizures.

Our understanding and clinical approach to the syndrome of cerebral apoplexy has in recent years undergone a remarkable evolution due to better knowledge of the pathological processes, refinements in diagnosis by cerebral angiography and pneumography, improvements in surgical technics and the discovery of drugs that permit the effective control of cerebral edema. Clearly we can no longer be satisified with a diagnosis of stroke or cerebrovascular accident, based solely on history and physical examination. Rational management cannot be instituted with these criteria alone. We need also diagnosis by cerebral angiography and assistance by the vascular surgeon.

L.H.N.

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Having Been Dead And Reborn

The coronary care unit (CCU) has come into existence primarily to enable us to recover patients who develop cardiac arrest, ventricular tachycardia and ventricular fibrillation, but who once resuscitated hopefully will go on to full recovery. People that experience cardiac arrest must face this experience suddenly and probably are not prepared to handle this experience psychologically. How do they handle this experience, initially in the CCU itself with death and dying emergencies and serious illness continually about them? How do they react to the unique and remarkable experience of having been "dead" and returned to life? This is an experience for which there is no prototype. What effect does this experience have on the future lives of these patients? These questions need an answer and Druss and Kornfeld[1] have tried to find the answer from a study of ten patients who survived cardiac arrest and ten others who were in the CCU but did not suffer arrest.

The procedures in the CCU needs no elaboration. Each patient has an intravenous needle in place, ECG electrodes on the chest. Many are receiving o^2 by mask or nasal tube and have indwelling bladder catheters, a recognized disrupter of sleep and mental health.[2] Vital signs are taken hourly. In the older units, patients are separated by curtain only. They can hear and at times see the other three. There is a clock in the room, shades are drawn, the door is kept closed, visitors are kept to one per patient for a few moments. There is a nurse in either monitor unit or across the corridor in which monitoring equipment records vital data.

An emergency of a serious nature occurs at least once a day, involving four to five staff members with much scurrying and excitement. When a patient has an arrest, it is terminated by violent motions of external cardiac massage, by the violent jolt of an electric current or hasty insertion of an internal pacemaker. Deaths are frequent occurring on the average one in four days. The atmosphere is one of darkness and quiet. Each patient, when awake, is able to see, hear and smell the life and death struggles of three other human beings and see the tracing of their heart beats on the machines above their head. The atmosphere is one of severe sickness. There is no interaction between patients. Often they look old and moribund. As soon as one gets better he leaves and a new, very sick one comes in to take his place.

Of the ten resuscitated patients, nine had a mild to severe organic brain syndrome, with symptoms ranging from restlessness, irritability, confusion to disorientation, delusional thinking and uncontrollable agitation. Seven of the patients were management problems, four of a serious nature. The less disturbed were restless, the more disturbed, agitated. What part loss of dreaming sleep played in this psychotic response[2] and what part cerebral anoxia played in the production of this brain syndrome is not clear from these reports.

Not a single patient could face all the implications of the cardiac arrest. All called forth protective defense mechanisms to relieve the emotional impact of the experience. The most common defense mechanism was denial and isolation of affect.

A second was displacement—the patient facing every minor thing except the real experience. A third defense mechanism was projection—their relatives and friends were anxious not they! A fourth reaction was hallucinatory and delusional behavior—having a defensive and reparative purpose, a wish to be well and away from their illness. Most patients felt secure in the unit because nurses and doctors were always at hand when needed, but leaving the unit meant they were better and this pleased them.

There were also long term effects. The patients were aware of the full implications of their experience. Their attitude towards death varied from nothingness to dreams. Insomnia was common in nine out of ten. Tenseness, anxiety, restlessness and irritability, not sadness or despondency. They had trouble concentrating and experienced memory loss of recent events. Remarkably there was little difference in the psychiatric state of the arrest and non arrest patients. Eight of the ten non arrest patients also had insomnia and three, symptoms of a mild organic syndrome. The similarity between the psychiatric responses of the arrest and non arrest patients suggests that the environment of the CCU played a major role.[2] There were also modifications in life habits. Many planned major changes in their daily habits, avoid excitement, sexual relations, alcohol. Some began counting their pulses. Work was either given up or reduced. Some of these changes, of course, might wear off as life's demands progressed.

Obviously, a cardiac arrest is a sudden and frightening experience calling forth a variety of defense mechanisms. The psychological problems were serious in both arrest and non arrest patients but more serious in the former. They had intense unconscious fantasies concerning death though maintaining an unperturbed front. Dreams of violent death and aggression, sort of nightmares, abounded. They needed to repress their experience and this made communication difficult.

Certain changes consistent with the principle of sound management can now be derived to avoid many of the psychological complications in the survivors of cardiac arrest. Anxiety and its cardiorespiratory components, agitation and uncooperative behavior are not merely troublesome, they may be life threatening. Particularly is this so when disorganizing behavior leads to hallucination and delusion formation. The patients stated they would have preferred a larger CCU with less congestion. Keeping all monitoring equipment out-

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side of the unit itself and in an annex would be less frightening to the patients. Steps need to be taken to reduce interference with sleep.

There is little doubt that denial might be protective and necessary during the crisis period. However, it can contribute to later adjustment problems if it is permitted to remain. Patients are quickly relieved by the opportunity to talk about their concerns and the ideal time to permit this ventilation is before the patient leaves the hospital and establishes his new life pattern. The limitations of his future activity should be discussed in detail so that he will not go toward either extreme of too much or too little.

The survivor has unasked questions which should be answered by his physician and not by a psychiatrist and especially not by an interne who has much to learn about how properly to talk with patients. The patient must be specifically reassured about the arrest itself. They need to be told that their bodies remained alive during the time their hearts had stopped. The matter should be dealt with openly, honestly even with those patients who claim to know "nothing" about any arrest.

The prognosis in these cases, Druss and Kornfeld found, is realistically poor, and the continued threat to the patients life is a real one. Yet the physician can offer the support of his understanding along with his medical attention. The sense of isolation and uniqueness which follows the experience of arrest when bridged by an understanding physician can add greatly to the patients mental and physical well being.

What we need to remember are the serious factors in the patients environment and the disturbances which must be minimized. After cardiac arrest a life is saved but there is much more needed before the patient can return to physical and mental health if he ever does.

L.H.N.

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Complications In Duodenal Ulcer

There are complications of duodenal ulcer which emphasize our inability to successfully treat this condition. There are complications of medical treatment and there are complications of surgical treatment although much fewer than formerly because of our better grasp of the physiology of gastric secretion and our growing understanding of the pathogenesis of duodenal ulcer.

The frequency with which complications occur in a general community is unknown because we only see that special group who require treatment. On the whole bleeding, perforation, intractability, and complications of therapy are the ones discussed by Allan Cooke in the conference on ulcer at UCLA.[1] Bleeding was the commonest complication of duodenal ulcer present in the two patients presented and usually estimated to occur in 16 per cent of all peptic ulcer patients. Although ulcers may bleed at any time, they usually cause some distress before they do. Ihre and Muller[2] found an average of 4.7 years of symptoms before hemorrhage occurred.

Intractability is often the end result of a duodenal ulcer treated for many years. The symptoms when present are classical. There is a change in location, radiation and intensity of the pain. It goes now through to the back. It is no longer relieved by food or antacids. The patient reveals tenderness in epigastric region or over the spinous processes. He may get relief from sitting up or leaning forward. A cause of intractability may be hyperthyroidism or Zollinger–Ellison syndrome. Why ulcers become intractable is difficult to determine. Some degree of penetration involving the pancreas and biliary tract may occur in half of such patients.

The hazards of medical therapy are easy to understand. Anticholinergics are dangerous in pyloric obstruction and bleeding. They may mask symptoms and delay recognition of recurrence or complications. They may precipitate acute glaucoma and urinary retention. Estrogen can cause feminization. Gastric freezing is replete with hazards. The milk alkali syndrome[3] produces lethargy, constipation increase in serum calcium, mental confusion, psychosis and progressive renal failure which is reversible if detected early. Of course, the medical man sees only those patients with the more severe forms of ulcer disease since many patients who have ulcers never consult a physician for the problem. This may explain why medical complications are encountered as often as they are.

The surgeon, if he is not confronted by a threatening emergency, generally is concerned with the elective operation and has as indications, intractability, perforation, hemorrhage and pyloric obstruction. His problem is now to select the operation that will not only avoid an ulceration elsewhere, but also avoid some of the late physiological disturbances that are related more to the operation than to the ulcer itself. The major physiological problems that concern the surgeon are how to control vagal influences on the parietal cells and the volume of the parietal cell mass itself as well as removal of gastrin forming cells in the antrum. Radical gastric resection formerly employed has its drawbacks.[4] Difficulties relating to nutrition, the small gastric pouch syndrome, and the dumping syndrome are primarily responsible for many patients being unable to tolerate gastric resection well. They cannot eat enough and if the dumping syndrome is severe the patient is unable to take enough food to maintain his nutrition.[5]

Because of all these factors vagotomy was employed at first and now selective vagotomy to denervate the stomach only is a little more difficult but less injurious. An adequate drainage procedure is necessary. Gastroenterostomy does not always work and if wrongly placed or becomes stenotic then antral mechanisms can cause hypersecretion and further difficulty. With fuller recognition in the last few years of the importance of the antrum, surgeons began taking out the antrum as well as doing a vagotomy. Such a procedure removes both the antral and the vagal sources of stimulation of the parietal cell mass. It leaves the acid secreting cells behind so that the patient can use them when stimulated by food and it leaves a good reservoir in the stomach behind. If just the antrum is removed enough stomach is left behind to perform a gastroduodenostomy.

If the surgeon takes into account recurrences and mortality rates, he will treat the least satisfactory candidates for operation with vagotomy and pyloraplasty because it is followed by the lowest mortality, 0.5 per cent. However, it has a recurrence rate of 3.1 per cent. The lowest recurrence follows vagotomy and antrectomy but its mortality rate is two to three per cent. The wise physician, of course, will appraise each patient on an individual basis and on the basis of the criteria outlined above. He will tailor the operation to suit the patient.

Individualization of the operation to the patients needs is also demanded in his medical therapy. The physician has to attempt to evaluate the individual peculiarities of his patient. He may be a frustrated, apprehensive, seething man forced to the hospital while many other things are on his mind. He may be forced to drink milk every hour, a soothing regimen to some but nauseating to others. He may be made miserable by a soft diet but calm down with a steak. Is a soft diet so clearly efficacious in healing ulcers as to warrant our making some of our patients miserable?

How many of us have insisted on having a patient swallow barium just as he was beginning to feel calm and comfortable or awakened him every hour day and night to take his blood pressure or see whether or not he is still bleeding? How positive are we that our present regimen is so remarkably effective in healing ulcers, that we can neglect our patient as a person in the process? Can we not provoke gastrointestinal ulceration or erosion by vasoconstrictive agents whether they come from emotional responses or enter the body through intravenous administration? Is it not possible that making a patient with duodenal ulcer comfortable and relaxed insofar as his particular circumstances permit may be itself therapeutic by reducing his own sympathetic nervous system responses? While we cannot state so categorically this approach seems more merciful and at least considerate. It is challenging to the doctor and usually more productive of good rapport with the patient.

Some patients want to get well and will. He is the one who conveys to the doctor that he appreciates the care he has been given. Some patients need their illness and they will not get well whether the treatment is medical or surgical.

L.H.N.

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Localized Disorders In Myocardial Contraction

We habitually think of congestive heart failure as being the result of a failure of contractility in the heart as a whole, as a generalized disturbance of contraction of one or both ventricles. Nevertheless on second thought why can't abnormal myocardial contraction also be caused by areas of malfunctioning myocardium interacting with other areas of completely normal muscle. This can obviously occur in a heart with a post-myocardial infarction scar or in a heart with multiple areas of fibrosis interspersed among normal myocardial muscle. Papillary muscle dysfunction, frank ventricular aneurysm and hypertrophic subaortic stenosis represent other local disorders producing generalized ventricular dysfunction.

The possibility that uncoordinated contraction of the heart can result from such a combination of normal and abnormal muscle has, however, received little attention. One of the reasons for this doubtless is not lack of the concept but lack of advanced methodology that could demonstrate its existence in the living heart as well as the hemodynamic consequences of morphologic abnormalities.

The concept that disturbances in the temporal sequence of myocardial bundle contraction secondary to deletion of certain of these fractions of cardiac muscle fibers as a result of localized ischemia or fibrosis, was clearly stated by Carl Wiggers in 1925.[1] The evidence for such disorganized patterns of contraction was furnished by Harrison who published kinetocardiograms of subjects with coronary heart disease (CHD) and in fact applied the term "asynergy" to this condition in an important paper entitled "Some unanswered questions concerning enlargement and failure of the heart."[2]

The pathophysiology and treatment implication of myocardial asynergy appear quite complex. Asynergy is difficult to diagnose and quantitate clinically, often involves viable myocardium responding to positive and negative contractile stimuli and perhaps contributes to unwanted compensatory alterations in adjacent normal and diseased myocardium. Such localized disorders frequently affect regions that might otherwise be suitable sites for myocardial revascularization. For this, however, we must be able to assess where the damaged area is, its extent, whether the myocardium is still viable though ischemic.

The assessment of myocardial function within the asynergic region is clearly essential whether the correction could come from resection or revascularization. Furthermore, early recognition of arterial obstruction might, with appropriate medical therapy, delay or diminish the ultimate development of asynergic areas of dysfunction in patients with CHD who are still asymptomatic.

The opportunity to study CHD from these points of view stems largely from a single advance in methodology, selective coronary arteriography and cineventriculography which can be done at the same time. Utilizing these new techniques Gorlin and his group have succeeded in documenting the presence and assessing the significance of regional metabolic and functional myocardial disorders in seventy-eight patients of whom ten turned out to be normal. Of the remaining sixty-eight patients forty-four had asynergy and twenty-four had CHD with normal left ventricular motion (synergy).

They learned this from catheterizing the left side of the heart and coronary sinus, from selective cineangiography of the right and left side of the heart and from the electrocardiogram which helped to define zones of myocardial ischemia. They were able to assess myocardial lactate metabolism and relate it to ischemic regions in the myocardium. They were able to improve functional performance in most subjects by administering isoproterenol or epinephrin by infusion. They showed that areas of asynergy became more extensive after propranolol which antagonizes inotropic effects of sympathetic bioamines.

Direct inspection at revascularization surgery and also at post-mortem confirmed the presence of all anticipated zones and strikingly, such zones were often muscle instead of fibrotic scars. In one subject suffering from alcoholic cardiomyopathy the asynergy was definitely worsened after ingestion of ethanol.

Gorlin's studies are important. In the first place he demonstrated what could have been anticipated, that in asynergy there is a reduction in effectiveness of aortic ejection and a reduced stroke volume. This can occur in the presence of a normal sized heart. Sixteen out of his forty-four cases of asynergy had a normal sized heart with normal dimensions and yet were in failure. This can be improved by exogenously administered catecholamines and therefore this procedure may be helpful in the clinical management of certain patients with ventricular asynergy.[5]

The precise defects responsible for local asynergy can be several. In some cases asynergy could result because of loss of contractile components with replacement by fibrosis. In others normal muscle may be interspersed with both parallel and series arranged fibrosis. This may act as elastic elements impeding or diminishing effective shortening of the fibers. On the other hand the muscle may be structurally normal but inadequately activated owing to local disturbances in conduction of the basic depolarizing impulse caused by ischemia or prior necrosis. Then, of course, ischemia may cause ultra-structural changes in mitochondria, the sarcotubular system or in the actinomycin filaments or bridges. This would lead to disruption of the biochemical and biophysical integrity of the excitation contraction linkage.

There are further implications of ventricular asynergy. Why for example is heart failure present in one person with CHD and not in another? Asynergy could be the cause of a morphological change to account for this fact. One can speculate that such dynamic abnormalities in ventricular motion may occur suddenly in acute myocardial infarction and lead to acute cardiac failure and the picture of cardiogenic shock so often encountered and so poorly explained at autopsy.

All these careful studies which might lead to an occasional salvage of a CHD patient by improvement in our medical or surgical facility of course warrants our full consideration. We must not lose sight, however, of the urgent need to pursue the ultimate conquest of coronary atherosclerosis which will greatly reduce the need for the complicated studies involved in demonstrating asynergy and the location of the critically damaged areas in the myocardium that bring the condition about.

L.H.N.

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Letter To The Editor

To the Editor

Prevention of Cruelty to People

Medical doctors have the reputation of being non-joiners when it comes to societies of civic interest. A recent experience of mine proved to me that this assertion is not necessarily true.

In my long standing desire to fight effectively air pollution, noise pollution, disease producing pigeon droppings and feathers, continuous destruction of trees and lawns to make room for more and more parking lots (the modern land pollution), dirt and litter on the streets, including beer and liquor bottles on private lawns, rats as well as similar cruelties to people's health, I suddenly had the idea to create the Connecticut Society for the Prevention of Cruelty to People.

While I did expect a great number of people to join the Society with enthusiasm, it never dawned on me that my colleagues will be so glad to sign up as members of a society which is not purely medical. Much to my pleasant surprise, nine out of ten doctors, I bumped into, not only signed the list of membership, but accompanied the signing with such remarks as "I am 100 per cent with you", "This is like love and marriage", "How can anyone be against it?" etc. So much so that I collected in three weeks 150 doctors' signatures or about one out of four non-doctors' signatures. This definitely proves that when it comes to an issue which is very much in the people's interest, doctors are not exactly "cold-blooded" as many try to make believe they are.

The membership of the Society is growing every day and already its influence can be felt. The little publicity that was given to it in the Hartford newspapers already persuaded many of the pigeon loving ladies to stop feeding them. Undoubtedly, they were not aware of the role pigeons are playing in the spread of psittacosis and histoplasmosis. In my own vicinity the pigeon population diminished significantly.

For the benefit of the readers of this letter, I would like to make it known that anyone can become a member by sending a check of one dollar, annual dues, to the Connecticut Society for the Prevention of Cruelty to People, 193 Girard Avenue, Hartford, Conn. 06105.

Sincerely yours,
Marcel Thau, M.D.

279 South Marshall Street
Hartford, Conn., 06105

Letters to the Editor are welcome and will be published for informative and educational purposes as space permits. As with other material which is submitted for publication, all letters will be subject to the usual editing. Address all correspondence to: The Editor, Connecticut Medicine, *160 St. Ronan Street, New Haven, Connecticut, 06511.*

The Continued Hazard of Surgical Glove Powders

Raymond S. Holtz, M.D.

■ The subject of talc and starch irritation resulting in most operative complications and foreign body granulomata has appeared in medical literature for the past twelve years or more. Immediately after the harmful effect of these powders was noted, surgeons endeavored to avoid this hazard by washing their gloves pre-operatively. This practice was continued until U. S. Food & Drug Administration announced acceptance of Absorbable Dusting Powder U.S.P. as an innocuous substance. Following this, the pre-operative routine of washing gloves was no longer considered necessary and the practice was almost completely discontinued. The innocuity of this powder was apparently not as complete or minimal as believed.

Evidence of this fact was established on May 5, 1959, when Myers et al presented a paper to the Philadelphia Academy of Surgery in which they described three cases of starch peritonitis. Their findings were confirmed by results obtained in subsequent animal experiment performed on three dogs.

One week following the introduction of starch into the peritoneal cavities of two dogs, (the third dog was used as a control), they were laparotomized and found to have severe cases of starch peritonitis with foreign body granulomata, ascites and adhesions.

Based on the assumption that starch peritonitis may have an allergic background, specific carbohydrate stains for corn starch, also characteristic refractory properties in polarized light failed to reveal any evidence of corn starch allergy.

The case presented herein is one which the author recently encountered in his private practice. It emphasizes the fact that starch powders which are used at the present time by hospitals and glove manufacturers are not in all instances free from harmful effect.

Mrs. G. B. White, age thirty-eight, P2, G2, Ab.o was admitted to Mount Sinai Hospital because of dysfunctional uterine bleeding and left lower quadrant pain. All laboratory findings including tests for blood dyscrasia and endocrinopathy were negative. X-ray findings including G. I. Series, Barium Enema and I.V.P. were negative. Pelvic examination showed no unusual features. She was taken to the operating room where a D&C and examination under anesthesia were done. Pap smear was reported as Class I, endometrium was in secretory phase. Because of long-standing left lower quadrant pain, laparotomy was performed. An enlarged, fluctuant tube on the left side, typical of hydrosalpinx was removed. An incidental appendectomy was also performed. Postoperative recovery was uneventful and the patient was discharged on her seventh post-operative day.

Approximately three weeks later, because of sudden onset of nausea, vomiting, abdominal pain, distention and elevated temperature, she was re-admitted to the hospital. Uterine bleeding had also recurred. She was taken to the operating room for exploration and hysterectomy for intractable uterine bleeding. Upon opening the abdominal cavity all of the abdominal structures were found to be acutely hemorrhagic in appearance; blood-tinged ascitic fluid was present. The serosal surfaces of the small and large bowel, peritoneum, uterus and bladder were studded with millet-size tubercles simulating acid-fast involvement. There was no evidence of caseous necrosis. A total hysterectomy, right salpingo-oophorectomy and left oophorectomy were performed. No adhesions were noted. Post-operative recovery was stormy. Distention necessitated a Levine tube and antibiotic therapy. Recovery was progressive and the patient was discharged on her tenth post-operative day. Path report showed foreign body granuloma.

The author, like countless other surgeons who are of the opinion that glove powders are harmless, neglected to wash his gloves prior to the first operation. The development of starch peritonitis with foreign body granulomata was obviously the result of oversight. Since surgeons seldom have the opportunity of a second look, there can be little doubt that many stormy post-operative recoveries are the direct result of starch irritation. To prevent this, the gloves should be washed thoroughly in basin water, rubbing vigorously between the fingers with a gauze pad.

Hospitals and glove manufacturers are compelled to continue the use of starch powders and their derivatives since there is no satisfactory substitute at the present time.

The severity of post-operative symptoms resulting from starch irritation may vary to a considerable degree, some being unrecognized because of their minimal degree while others may approach those of shocking proportions. Inasmuch as this

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complication may produce symptoms of bizzare nature, a differential diagnosis may be extremely difficult or even impossible to make. As a result of this, laparotomy often becomes imperative.

The observance of this precautionary measure is a vital factor, not only in the prevention of surgical morbidity but in the avoidance of unnecessary suffering and expense on the part of the patient.

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On Making Ethical Decisions

We must come back to the medical decision in those disturbing cases where the doctor cannot hope to find a ready-made solution by established standards. We must define which factor in the last analysis would cause a doctor to make the final decision in such cases. It cannot be an order imposed by an external force as the preceding argument adequately proves. The final motive can only be inner and personal. The action of the doctor can be nothing else than the projection of the image which he has himself made of the external world, of the sick man and of the role of the doctor. A practical consequence follows immediately: The ethical training of a doctor cannot be limited henceforth to the teaching of a few ready-made rules; it should also encourage a lucid inner understanding of the relationship between doctor and patient, of the dignity of the latter and of the extent of the services which the former can offer. In this way will be developed more surely than by a code the deep sense of personal responsibility essential for every doctor.

To produce doctors who are strong men, who are not only honest and just in thought but efficient in action; to develop in them an awareness of the value of human life; to convince them that their vocation is an extensive obligation to the individual and to the group: such it would seem are the best means of facing the ever-increasing difficulties of medical ethics. Jean Hamburger in Ethics in Medical Progress. Ciba Foundation Symposium, edited by Wolstenholme, G. E. W., O'Connor, M. J. and J. A. Churchill, Limited London, and Little Brown and Co., Boston, 1966. pp. 137-138.

Meningococcemia

Leo Litter, M.D.

For many years Meningococcemia has been a treacherous disease to treat. Its therapy is still an unsolved problem.

The meningococcus, or Neisseria meningitidis, a Gram-negative diplococcus, gains entrance through the upper respiratory tract. A bacillemia follows and the subsequent course depends on the resistance of the host. If this proves to be low, septicemia is likely and localization in the meninges is particularly liable to occur.

Meningococcemia has a sudden onset, with high fever—105° F. or higher—twitching or convulsions—especially in infancy—marked toxemia and a spreading purpuric rash which may vary in degree from scattered petechiae to extensive ecchymoses. There may be profound shock, pallor and gasping respirations in severely affected infants, the so-called Waterhouse-Friderichsen syndrome. When this occurs the prognosis is grave, not more than 50 per cent recovering even with the best treatment. At autopsy, extensive bilateral adrenal hemorrhage is found.[1]

A severe case of meningococcemia in a 2½ year-old child, who responded well to a comprehensive therapeutic regime, is presented.

Meningococcemia

J. J., 2½ year-old, white male child was admitted to St. Francis Hospital because of fever, vomiting and rash.

H.P.I. He had been apparently well until one week prior to admission when he developed fever and cough associated with bouts of drowsiness and diarrhea. He improved temporarily for 2 days on ASA and remained afebrile for the next few days. One day prior to admission he again developed high fever with vomiting. He was seen by his pediatrician who advised hospitalization but the parents were reluctant. The child was brought home and 3 hours later developed a rash over the upper chest, lower abdomen and upper thighs with persistence of high fever (105° F.), vomiting and irritability. The pediatrician was called and referred him for admission. History of exposure to contagious disease or possible drug ingestion denied.

Past History. Birth weight 6 lbs. Neonatal course uneventful. Development normal. Immunizations: routine. Has had measles and febrile convulsions at 1 year of age. No history of allergy or previous operations.

Family History. Youngest of 8 children. Sibs doing well.

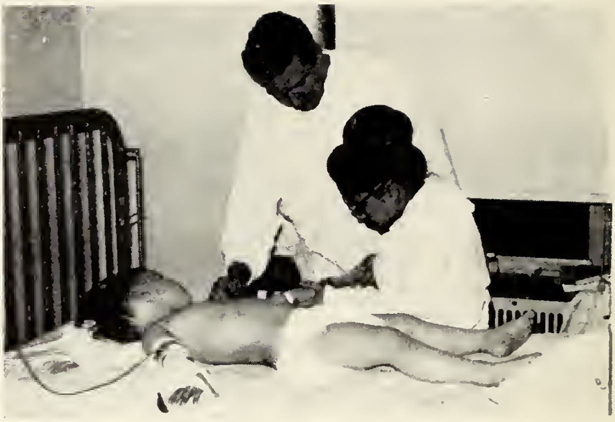

Figure 1

Critically ill patient being examined immediately upon admission.

Physical Exam. Well-developed and nourished, but somewhat lethargic, dehydrated, highly febrile white male child weighing 33 pounds. Temperature 105.6° F.

Head—fontanels closed. No scars.

EENT—Eyes—no nystagmus, small subconjunctival linear hemorrhage of left eye. Pupils equal, round and reactive. Fundus normal. Eardrums—minimal peripheral congestion. No nasal discharge no epistaxis. Lips are dry and parched with dark material coating the gums. Tongue dry and coated white. Tonsils enlarged, no exudate.

Neck—supple with few palpable cervical lymph nodes.

Chest—symmetrical with equal expansion of pulmonum.

Heart—regular sinus rhythm. 160/min. Pulse full and bounding. No murmur. Blood pressure 90/40.

Lungs—clear, respirations 60/min.

Abdomen—flat, soft. Liver edge, sharp and 2 cm. below right costal margin. Tip of spleen palpable. Generalized tenderness on deep palpation without any muscle guarding or rebound. Bowel sounds good.

Extremities—marked tenderness on knee, ankle, elbow and wrist joints without any swelling or redness.

Skin—maculo-papular rash, discrete over the face, neck, upper anterior chest, lower abdomen, buttocks and thighs.

Neurological—conscious, oriented, lethargic. Babinski's positive bilateral.

Laboratory Results: (2nd day) Bleeding time 8½ minutes.

Coagulation 11½ min; clot soft, retraction normal.

pH of whole blood 38° C. -7.48.

DR. LEO LITTER, Attending in Pediatrics, Mt. Sinai Hospital, Hartford, Conn.

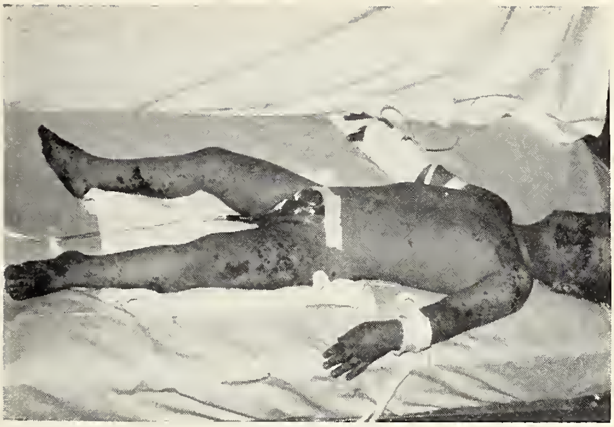

FIGURE II

Diffuse petechial hemorrhage typical of this disease.

Serum Electrolyte	*NA*	*Cl*	*CO_2*	*K*
(1st day)	137 meq/L	105 meq/L	15 meq/L	3.4 meq/L
(7th day)	141 meq/L	99 meq/L	22 meq/L	4.9 meq/L

Blood type O Rh +

Total proteins 6.7 gms. % A/G 2.6/4.1 (8th day)

Blood cultures (1st day) Neisseria meningitidis Serologic group B

Sensitive to Sulfa, Penicillin, Tetracycline, Panamycin, Polycillin, Streptomycin, Erythromycin, Chloromycetin.

(20th and 28th day) negative.

Blood sulfa levels 15.3 mgs% (2nd day)
8.8 mgs% (5th day)

BUN 7 mgs% (18th day)

Spinal Fluid (1st day) clear, colorless, no cells seen.

Sugar 115 mgs% Protein 17 mgs% Chlorides 128 meq/L

Smear-no organism Culture-no growth

Sedimentation rate	2nd day	5th day	11th day	24th day
	1 mm/hr.	48 mm/hr.	80 mm/hr.	26 mm/hr.

Prothrombin time— 11% of normal (2nd day)
37% of normal (3rd day)
100% of normal (24th day)

Urine culture—negative.

Series of urinalysis and sulfa crystals—negative.

Stool for occult blood positive on 3rd, 5th, 10th, 11th, 13th through 17th day.

EKG (2nd day) normal.

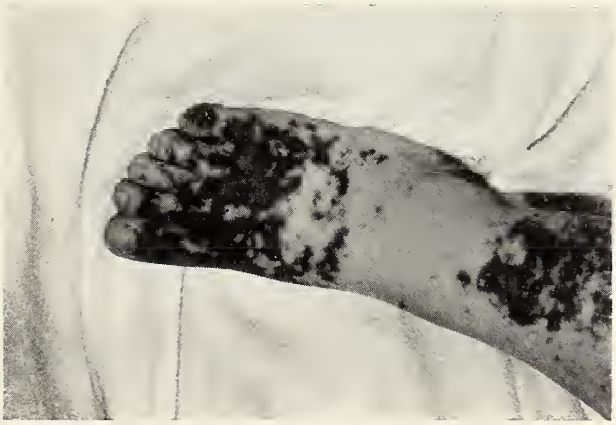

FIGURE III

Closeup of petechial and ecchymotic lesions on right foot.

Peripheral Blood Counts

Day	1st	2nd	3rd	25th
WBC	5,100	18,800	27,900	5,500
Neutrophils	75%	74%	90%	52%
Lymphocytes	15%	11%	3%	33%
Atypical lymphocytes	0	0	1%	4%
Monocytes	6%	11%	5%	5%
Metamyelocytes	3%	4%	1%	0
Eosinophils	1%	0	0	6%
RBC	4,220,000	5,520,000	4,460,000	—
Hemoglobin	7 gms.	9 gms.	8 gms.	11 gms.
Hematocrit	26%	32%	27%	38%
Nucleated RBC	11%	0	0	0
Hypochromia	3+	2+	2+	2+
Microcytosis	3+	2+	2+	1+
Basophilic stippling	1+	0	0	occ.
Poikilocytosis	1+	1+	occ.	occ.
Eliptocytosis	0	1+	few	0
Platelets	Increased	88,000/ cu. mm.	Decreased	Slightly increased

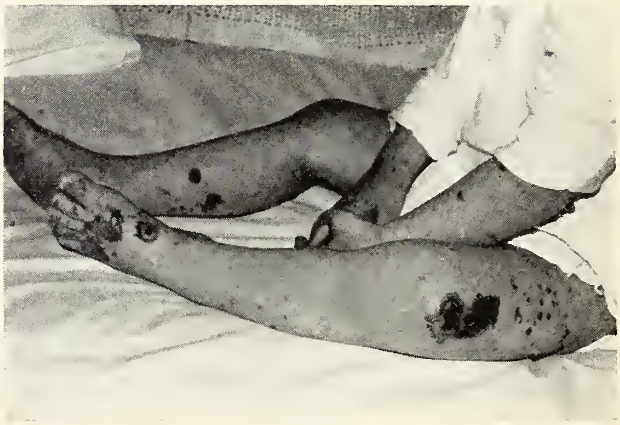

FIGURE IV

Several days following medication, healing is progressing. Lesions were more pronounced on the left side.

Course in the Hospital—Initially vital signs were stable. Immediately upon admission blood for culture was obtained. Intravenous fluids were started with Penicillin and sulfa diazine therapy. After an hour, blood pressure dropped to 50/30. The skin eruption became purpuric and increased in intensity and progressively extended.

Whole blood and steroids were administered. Blood pressure rose to 110/50-70 and vital signs remained stable.

After 4-6 hours the whole body, especially the extremities, chest and face, was covered with large areas of purpura. Condition remained the same for the next 12 hours. Temperature dropped to 101°F. Blood culture grew Neisseria meningitidis in 24 hours.

On the second day he developed a distended abdomen with stools positive for occult blood and low prothrombin time. At this time the Aspirin was discontinued and Tylenol substituted. Chloromycetin, Vitamin K and C were added to the therapy. Lactinex therapy was started to prevent over-growth of yeast, monilia, and staphylococci.

He improved for the next 6 days with drying up of the skin lesions, diminution of abdominal distention and negative blood in stool. After 1 week he again started spiking fever to 101-102° F. and on the 9th day to 104° F. At this point all medications were discontinued and blood, urine cultures were repeated.

Hemoglobin dropped to 6.5 gms. on the 12th day and another blood transfusion was given. Repeat cultures were negative.

On the 2nd week of hospital stay he was ambulatory with areas of sloughing over the left knee, both feet and leg.

After the 3rd week, Chymar ointment was applied to areas of sloughing over the left upper and lower extremities. Three days later, good healing and softening were noted on the left side. The hospital staff was much impressed with the more rapid healing response of the sloughed areas to Chymar ointment.

On the 4th week, debridement was performed. Repeat blood studies showed patient to be much improved. Hemoglobin remained at 11 grams and prothrombin rose to 100% of normal. Skin grafting over the denuded areas was performed on the 36th day of illness, and child was discharged several days later.

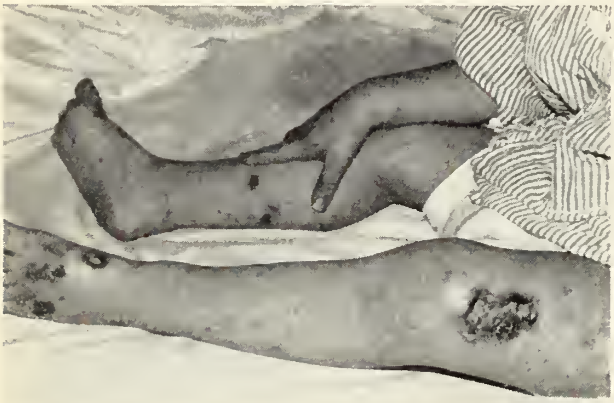

Figure V
Chymar ointment is used on the left lower extremity.

Summary of Medications Used

Aqueous Penicillin I. V. for 3 days.
Sulfadiazine I. V. for 3 days.
Oral sulfa and penicillin for next 6 days.
Chloromycetin 48 hours.
Solu-Medrol I. V. for 5 days, then Meticorten for ten days.
Vitamin K and C
Iron, orally
Amphogel, Pyribenzamine
Chymar ointment
Parenteral Fluids: 1) Normal saline with Dextrose and KCl
2) Baxter's Electrolyte No. 75—5%
Blood transfusions
Lactinex

Comments

The clinical syndrome of meningococcemia is rather characteristic. Seventy per cent of the cases affect children below the age of two. The disease starts suddenly with nausea, vomiting, headache and fever, followed by deep cyanosis alternating with marked pallor. The sensorium becomes clouded and convulsions occur in some cases. After a few hours, petechial cutaneous hemorrhages appear and increase rapidly in number and size, before fusing into large suffusions. Sanguineous saliva and diarrhea indicate mucosal hemorrhages. In addition, livid discoloration of large areas may appear.

There may be severe shock with an almost imperceptible pulse and hyperpyretic temperatures while the blood pressure may be unobtainable. The patient then loses consciousness and usually succumbs in a deep coma within 10 to maximally 48 hours. The blood smear shows usually a shift to the left and only a slight elevation or even a reduction of the number of leukocytes. Rare findings include a diminution of the platelets, hypoglycemia, hyponatremia and hyperkalemia.[2]

In typical cases the spinal fluid is free of albumin and at most shows a minimal increase of the cells. The diagnosis is established by the demonstration of the meningococcus in spinal fluid, blood, bone marrow or scarified cutaneous hemorrhages.

The stress situation of an acute severe infection places an increased demand on the suprarenal cortex. Cortisone administration may represent merely symptomatic therapy with an antitoxic, antiphlogistic and anti-allergic effect.

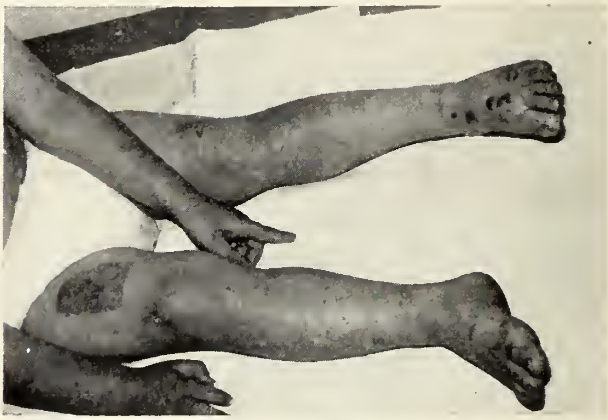

Figure VI
Rapid healing of lesions on the left side. Skin graft—right upper thigh.

It is the feeling of the author that whereas the place of antibiotics has firmly been established in the treatment of meningococcemia, optimal management demands the addition of adrenal steroids in adequate dosage.

Figure VII
Patient well on discharge.

Summary

A case of fulminating meningococcemia with recovery is presented. Details of management resulting in a favorable outcome are discussed. The favorable outcome of this case may be partly attributed to the deep personal interest of the St. Francis hospital house staff.

Comprehensive therapy consists of many facets. Circulatory failure was treated with fluids, electrolytes and small transfusions of blood. Since some strains of Group B meningococci are resistant to sulfonamides, pending results of the antibiotic-sensitivity tests, large doses of penicillin were also administered. Therapy also included Lactinex to prevent outgrowth of pathogenic organisms, Amphogel to prevent gastric mucosal irritation by the steroids, Vitamin C and K to bolster the vascular system and Chymar Ointment to hasten healing of the sloughed skin areas.

Acknowledgments

My gratitude to Dr. Diane Yadao, senior resident in Pediatrics, St. Francis Hospital, Hartford, Connecticut, without whose help this case might have terminated unfavorably and to Dr. Daniel Marshall for his assistance in the preparation of this manuscript.

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Sage Counsel To Graduates Of 80 Years Ago

He (the recent medical graduate) should never forget that medicine, like all knowledge, has a past as well as a present and future, and that in the past is the indispensable soil out of which improvement must grow. He should remember, too, that however closely related the several branches of medicine are to one another, each one in its turn is best learned by an almost exclusive devotion to it for a time, and when his barns are filled to bursting with his harvest, let him not forget that the grain has still to be winnowed. His fan must be in his hand to purge the threshing-floor of the dead, the unessential, the hypothetical, the fanciful, and, above all, the false. In all things truth must be his object, his inspiration, and his guide.—Stillé, A.: Address Delivered to the Medical Classes of the University of Pennsylvania, *Med News* 44:433-438, 1884.

A Follow-up Evaluation of Lumbar Disc Surgery

A. D. Greenberg, M.D. and S. Flanigan, M.D.

Mixter and Barr published the paper on the original surgical management of a ruptured intervertebral disc in 1934[3]. Since that time large series have reported surgical results. This is a review of the lumbar discs operated at the Veterans Administration Hospital, West Haven, Connecticut, from 1954 to 1964. In this ten year period 350 patients were operated with a diagnosis of a ruptured lumbar disc. A questionnaire sent to these patients consisted of 35 questions which could be answered affirmative or negative. The questions were designed to define the patient's impressions of his experience with the lesion and the surgery for it. The report is based on 112 responses to the questionnarie. All but two of the patients were males and the ages ranged from 27 to 73 years with an average of 44 years. In 51 patients (46 per cent) the L5 disc was removed; in 49 patients (44 per cent) the L4 disc was removed; L3 disc disruption was encountered in only four patients (4 per cent); five patients required excision of both the L4 and the L5 discs; and in three patients (3 per cent) no disc abnormality was found. An immediate family history of "disc trouble" was acknowledged in 14 per cent of those reporting. Forty-four patients had experienced neck or arm pain in addition to the sciatic and low back pain.

Ninety-nine patients (88 per cent) indicated that they had had relief of pain with the operative procedure for the removal of an offending ruptured intervertebral disc. At the same time almost as many patients (96) still had some discomfort. Among the latter, 27 indicated occasional low back pain, 13 responded affirmatively to persistent or recurrent leg pain, and 56 others acknowledged some residua of both symptoms. The persistent pain was of the same nature as that prior to surgery in 33 patients (29 per cent) although the majority responding so indicated less severity of the pain. Sixteen patients (14 per cent) felt that their pain was greater at the time of reporting than it had been before the surgery. More than one operative procedure was undertaken in 21 patients (18 per cent) and among these a larger number felt that there had been no relief with surgery.

One-third of the patients responding to the questions indicated that they had been unable to work for a period of more than six months prior to the operative procedure. Twenty-seven patients (24 per cent) were unemployed at the time of the inquiry and almost all of these had been unable to resume their usual or any work in the six months following the operative procedure. A third of the patients attributed their disc problems to the type of work they were doing. Forty-eight patients (43 per cent) were doing lighter work than that in which they were occupied before this surgery. All but one of this latter group attributed the change in their occupation to the problem which they had suffered with the lumbar disc. Nearly half of the patients stated that they were still losing work because of the disc problem. Sixty-five patients had used a lumbosacral support at some time before or after the surgery and 60 per cent of these patients felt that it had provided them some relief.

On the basis of responses to the questionnarie patients were grouped as improved or unimproved with operative intervention. Only 14 per cent of the patients reported that they were no longer having any discomfort. When re-operation had occurred no one of the patients considered himself "cured". Even the number who acknowledged relief with the surgery dropped from 91 per cent in those who had undergone a single operation to 76 per cent in those who had been operated more than once. Three times as many patients who were operated more than once were classified as unimproved, but there was no greater incidence of unemployment in this group. Twice as many of those who had undergone multiple operations attributed their disc trouble to their work. The level of disc disruption bore no correlation with the blame of the difficulty on the occupation.

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The results of this study were compared to the series of 1176 patients reported by Gurdjian et al[2], and the 413 male patients reported by Brown and Pont[1]. The incidence of poor results or patients reporting an unimproved condition were comparable in each of the series. The number of patients reported "cured" was greater in both the Gurdjian and the Brown and Pont series. When the latter series was subdivided so that results were reported on the one hand for those patients which were private and on the other for those which were industrial workers, the figures for the industrial worker group were very nearly comparable to those obtained in the survey of the Veterans Administration patients. There was a greater number of patients at the Veterans Administration hospital who were operated more than once and in keeping with the other two series these patients did not fare as well as those undergoing only one operative procedure. In Gurdjian's series only three per cent of the patients operated more than once became symptom free and 24 per cent were considered "poor results".

It becomes apparent that patients operated for lumbar disc disease can expect palliation but in general should not anticipate a complete cure from their symptoms. The operation is a procedure for relief of symptoms but a substantial number of patients continue to have an awareness of the difficulty for which they underwent the operative procedure. In general these residual symptoms are not sufficiently severe to be brought to the attention of the physician and can be accepted by the patient provided he is not seeking a "cure".

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High Living and Air Pollution 300 Years Ago

True Old Parr is said to have lived 152 years and nine months and to have married a widow when he was 120 years old. Even at this age prosperity overcome him. The autopsy report by Dr. Harvey, November 6, 1635, says "in short all his inward parts appeared so healthy that if he had not changed his dyet and air, he might perhaps have lived a good while longer. But coming out of a clear, thin and free air into the thick air of London and after a constant plain and homely country diet, being taken into a splendid family (of the Earl of Arundel) where he fed high and drank plentifully of the best wines; whereupon the natural functions of the parts of his body were overcharged, his lungs obstructed and the habit of the whole body quite disordered, upon which there could not but soon ensue a dissolution."—From Editorial by Howard Sprague—*Circulation.*

Maternal Rubella And Hearing Loss:

A Preliminary Report on Findings from the 1964 Epidemic

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It is well recognized that maternal rubella during early pregnancy may cause serious developmental anomalies in the fetus. A triad of symptoms in the newborn including cardiac defects, congenital cataracts and hearing loss was related to this disease by early investigators[1], [2], [3]. Neonatal studies following the 1964 rubella epidemic in this country have revealed a number of additional manifestations which may occur in isolation or in any combination[4]. Any one or combination of these congenital abnormalities may adversely influence the young child's development.

While a bilateral auditory impairment has long been recognized as one potential sequela of maternal rubella, neither the frequent incidence nor the pervasive effects of such an impairment have been stressed. For this reason, the purpose of this paper is two-fold:

1) to review past studies concerned with the relationship of congenital hearing loss and maternal rubella, and
2) to present pertinent case history information and the audiological findings for a sample of children with an etiology of maternal rubella stemming from the 1964 epidemic.

Review of Literature

Implication of the rubella virus as a cause of birth defects is credited to an investigation by Gregg in 1941[1]. By 1949, hearing loss was clearly established as one of the more common sequelae of the disease[5]. Further, it has been noted that an auditory impairment results most frequently when the onset of the rubella rash in the mother occurs between the sixth and ninth week of pregnancy. In other words, the relative risk of such an auditory impairment appears to be highest during the second month of gestation, a time which corresponds to rapid cellular differentiation in the fetal cochlea.

The exact incidence of hearing impairment among rubella babies is not well established. For example, estimates range from a low of 2.8% to a high of 52% [6],[7]. A number of variables including test procedures, sophistication of the tester, criterion for hearing loss, etc., may account for such a wide variance. Another important factor may be the age of the subject when tested. It is of interest that longitudinal studies find a marked increase in the incidence of rubella hearing loss with increased age. Giles, et al., reported that only 27% of their hearing-impaired rubella subjects were identified as having a hearing loss by 18 months of age[8]. A number of partially-hearing children were not identified until the age of five. Since partially-hearing youngsters characteristically respond to some of the louder environmental and speech sounds, a hearing loss is not suspected. They are often labeled as 'slow talkers' and are not referred for hearing tests until it is obvious that their communication deficits will preclude normal school placement.

Two factors, in addition to the variables mentioned above, could account for the increased incidence of hearing impairment in older rubella children. On one hand, the rubella child is as susceptible to middle ear infections with an increase in hearing loss, as are other preschool youngsters. In fact, Hopkins[9] found that 13 out of 92 rubella patients had a history of otitis media, a proportion which was somewhat greater than reported for the siblings of these same patients. (Of course, additional impairments may result also from any one of the host of etiological factors which cause a hearing loss during childhood). On the other hand, some investigators have speculated recently that additional damage to the auditory mechanism may result postnatally since some subjects have been found to be actively infected with the rubella virus following birth[10], [11]. In either instance, an in-

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creased incidence of hearing impairment among older rubella children should be anticipated. To summarize, while statistics regarding incidence do vary, most researchers conclude that hearing losses are a good deal more frequent in samples of rubella babies than is generally suspected.

The initial report by Murray in 1949, indicated that the hearing loss related to maternal rubella was sensori-neural in type, i.e., a dysfunction of the inner ear and/or eighth cranial nerve[5]. Further, both ears were involved in the vast majority of the subjects. These clinical observations were later substantiated by Fisch in England and Goodhill in the United States[12], [13].

While temporal bone studies of hearing-impaired rubella cases are limited, the available histologic studies have revealed cellular changes primarily in the cochlear structures[14], [17]. Among the changes noted were poor differentiation of the hair cells, cytoplasmic destruction in the organ of Corti, and a demonstrable reduction of blood vessels in the stria vascularis of the inner ear. Thus, the limited number of temporal bone examinations indicate that the site of lesion underlying the rubella hearing loss is in the inner ear; a finding which had been inferred from earlier audiological studies.

The average degree of hearing loss at those frequencies important for the perception of speech has been found to be substantial in most instances. Murray's data revealed that the average loss for his sample was 65 dB in the better ear[5]. Hardy reported an average loss of 58 dB for a sample of rubella cases[18]. In both studies, the degree of hearing loss would be classified as moderate in severity. Of course, it should be recognized that a hearing loss due to most etiologies can range from mild to profound. Goodhill's findings reveal that such a variation in severity does occur with a sample of rubella cases since a range of hearing loss from 20 dB to 100 dB was observed[13].

Most investigators have further noted that regardless of the degree of impairment, some residual hearing is found across frequency. In other words, the impairment is of similar magnitude for the several frequencies routinely tested during pure-tone audiometry. Therefore, the audiometric configuration reflected by the pure-tone audiogram is typically described as a flat profile. This configuration is in sharp contrast to the precipitous pure-tone configuration encountered in many congenital impairments, where there is little if any hearing for the higher frequencies which carry important acoustic information needed for the perception of speech.

The findings from past studies of congenital auditory impairment due to the rubella virus can be capsulized in the following manner. First, a hearing loss of substantial magnitude in both ears is usually encountered. While such losses may occur in as many as 50% of all rubella babies, such impairments may escape detection until the child is older unless audiological assessments are scheduled from an early age. Finally, both audiologic and histologic studies indicate that the most probable site of dysfunction underlying the auditory impairment is in the cochlea.

Clinical Procedure and Findings

A sample of thirty two children with a history of maternal rubella and suspected hearing loss was evaluated during 1966 in the University of Connecticut (UConn) Hearing Clinics at either the Hartford Hospital or the Newington Hospital for Crippled Children. The average chronological age of these youngsters at the time of the initial assessment was 22 months. Prior to the audiological evaluation, specific case history information was obtained regarding the time during pregnancy that rubella was contracted, the child's birth weight, the rate of motor development and the incidence of associated anomalies.

While the subjects' young age precluded the utilization of formal audiometric techniques, valuable information was obtained regarding auditory status by presenting calibrated acoustic stimuli into a sound-treated test environment. Behavioral observation audiometry (BOA) was first employed to establish the minimal intensity at which consistent auditory responses were observed. The acoustic stimuli for this test included recorded environmental sounds, monitored live-voice presentations, and the noise generated by various sound toys. Responses of the child to such sound presentations included cessation of activity, a startle response, scanning of the environment and/or localization of the sound source to one of the loudspeakers. Since many of the test signals contained multiple frequencies, only the general degree of hearing loss could be determined. In other words, precise information regarding auditory deficits at specific frequencies could not be obtained. For this reason, conditioned orientation reflex audiometry (COR) as described by Suzuki and Ogiba was also utilized during the evaluation[19]. With this technique, the child is conditioned to anticipate a visual stimulus immediately following the presentation of an acoustic signal. Once conditioned, the subject responds to the auditory presentation, if heard, by turning toward the potential source of light. The tester then reinforces this anticipatory behavior by flashing a light which has been incorporated into an attractive toy. With this procedure, it is possible to present various pure tones with a 5% frequency modulation in the sound field and thereby obtain estimates of the patient's auditory acuity across frequency. Information regarding the patient's pure-tone configuration is highly advantageous in terms of selecting a hearing-aid with the most appropriate frequency response to compensate for the youngster's auditory impairment as well as formulating a realistic prognosis of the speech and language development to be anticipated. It was found that with a battery of pediatric hearing tests, including both BOA and COR audiometry, information could be obtained which facilitated patient management and habilitation even though the average age of the children was 22 months.

Case History Information

The case history information revealed that the mothers of the subjects contacted rubella during a period that extended from four weeks prior to conception to 14 weeks into pregnancy. It is noteworthy that in two-thirds of the cases the onset of the disease occurred between the 5th and the 8th week, with the median being the seventh week. This central tendency is in agreement with the findings from past investigations which have indicated that the first trimester, or more specifically, the second month is the time that hearing impairment most frequently results from maternal rubella.

The birth weight of the subjects was of interest since low birth weight has been reported as a common finding with rubella infants. The birth weight for the sample of subjects under study ranged from 3 pounds 8 ounces to 7 pounds 5 ounces, while the median was found to be 6 pounds 2 ounces. It is interesting to note that during the case history, several of the mothers remarked that the child in question was much smaller than his siblings had been at birth. For this reason, the child's relative as well as his absolute birth weight may be of interest. Whether viewed in terms of absolute or relative birth weights, the subjects in this study tended to follow the reported trend of being lighter in weight at birth than the average neonate.

While many of our subjects had various anomalies and signs of the rubella syndrome, only those symptoms of the classic rubella triad are reported here. Four categories were established based on 1) hearing loss, alone; 2) hearing loss with cataracts; 3) hearing loss with cardiac defects, and 4) the classic triad of hearing impairment, heart defects and cataracts. The findings from our study are displayed in Table I. (One child who had a questionable hearing loss is not classified in this breakdown).

Table I

Incidence of Anomalies in a Sample of Children with a History of Maternal Rubella (N=31)

ANOMALY	NUMBER
Hearing loss, alone	22
H.L. with cardiac defect	7
H.L. with cataracts	1
Triad of anomalies	1

Barr and Lundstrom reported their data by similar categories and in terms of percentage of their sample. The parallel trend found in their report from Sweden is striking. For this reason a comparison of their findings with those of the present study is presented in Table II.

Table II

Comparison of the Incidence of Anomalies Reported in Percentages noted among children with a history of Maternal Rubella by Present Investigators and by Barr and Lundstrom

ANOMALY	UConn	Barr & Lundstrom
	(%)	(%)
Hearing loss, alone	72	82
H.L. with cardiac defect	22	16
H.L. with cataract	3	0
Triad of Symptons	3	2

These two studies suggest that the chances of a child being born with a hearing loss as part of the complete triad are relatively low. Further, his chances of having a hearing loss in combination with congenital cataracts is also minimal. However, the possibility of having both hearing loss and heart abnormalities is considerably higher. Finally, it is evident that the majority of the cases in both studies have only a hearing impairment rather than the classic rubella syndrome.

A relatively high occurrence of mental retardation in rubella children has been reported[20]. While psychological testing had not been undertaken with the children under study, it was disturbing to note that delayed motor development was reported in about one-third of the cases. Such cases will be referred for psychological evaluations since Barr reported that 32% of his subjects were ultimately classified as slow learners. Of course, a positive relationship between delayed motor maturation and mental retardation is not always established. However, delayed motor maturation is indicative of mental retardation often enough to warrant referral for a psychological evaluation in such cases.

The range of hearing impairments noted during the present investigation varied on a continuum from mild to profound in degree. Table III reveals that the majority (75%) of the impairments fall into either the moderate or severe categories. The median hearing loss was found to be 72.5 dB (re: ISO norms). This degree of loss is quite similar to that reported in a number of prior investigations.

By utilizing the COR technique it was possible in a number of instances to obtain pure-tone responses (usually at 500 to 4000 Hz) across frequencies. In most cases such results indicated that the configuration of the losses was relatively flat. In other words, the child appeared to have some residual hearing across the frequency range.

To summarize, it appears that hearing loss subsequent to maternal rubella may run the gamut from a slight impairment to a profound loss. (See Table III). However, the majority of the impairments fall into the moderate to severe range, with the impairment being approximately equal across frequency.

TABLE III

CATEGORIZATION OF THE HEARING IMPAIRMENTS NOTED IN THE PRESENT STUDY BY DEGREE OF LOSS

DEGREE OF HEARING LOSS	N	%
Mild (50 dB or less)	5	16
Moderate (51-70 dB)	11	34
Severe (71-90 dB)	13	41
Profound (greater than 90 dB)	3	9

As mentioned earlier, several authors have reported that an increased incidence of hearing loss is noted when a sample of rubella children are retested over time. For this reason, the present sample may be biased in that an unknown number of children with mild to moderate hearing impairments resulting from the 1964 rubella epidemic may yet need to be referred for an audiological evaluation.

Comments

The audiological results obtained with the present sample of children indicate that a significant (50 dB or greater) bilateral hearing loss was present in 84% of the subjects. Significant hearing loss is used in this context as an impairment which will result in a marked delay in speech and language development. Further, the findings revealed that the auditory impairment most frequently occurred in isolation rather than as one component in the classic rubella triad.

It is well established that early identification and habilitative management during the preschool years are a necessity if the pervasive effects of a congenital hearing loss are to be minimized. An auditory impairment resulting from maternal rubella is no exception. For this reason the availability of wearable amplification and the initiation of remedial training should be provided for preschool children as early as possible. Therefore, the importance of referring the very young patient with a suspected hearing loss resulting from maternal rubella to a speech and hearing center cannot be overstated.

The widespread belief that hearing tests cannot be successfully administered to the child under 5 years of age is negated by the results presented for the present group of rubella youngsters. Repeat audiometry has now been completed in most cases and the initial results were found to be remarkably accurate despite the child's very young age during the initial evaluation. Needless to say, periodic audiological re-evaluations during the preschool years are desirable since more sophisticated tests and measures can then be employed as the child matures. Such detailed information makes it possible to adjust the hearing aid for the best possible response and to modify the remedial program to meet each child's special needs.

A popular misconception among physicians which often delays early habilitation is that the person with a sensori-neural hearing loss is not a candidate for hearing-aid use. While there are limitations in aided listening for such patients, the advantages of hearing-aid utilization far outweigh the disadvantages. Without wearable amplification, the majority of the rubella children in this study would be out of contact with the world of sound, which leaves the visual sensory modality as the only available means for developing communicative skills. Many clinicians now feel that maximum growth in speech and language can be realized only if the child utilizes his residual hearing in conjunction with visual communication. For this reason, the selection of a suitable hearing aid for each of the young children in this sample has been a major clinical objective. Since the majority of the cases appear to have some hearing even for the high frequencies, the rubella child appears to be a good candidate for hearing-aid use. The progress reported by parents and therapists during the past few months testifies to the validity of this statement.

Finally, the findings obtained do not appear to justify the classification of many hearing-impaired rubella children as 'deaf'. While a number of cases do have a severe to profound loss of acuity, at least 50% of the sample are more accurately classified as partially hearing rather than as deaf. Such a classification is especially important when educational placement is considered. The ultimate goal for the partially-hearing child should be integration into the regular classroom. Unfortunately, many children who are partially hearing are placed in a residential school for the deaf and consequently never realize their maximum potential either in the development of communicative skills or in academic achievement since their residual hearing is not capitalized upon.

Summary

The results from the audiological evaluation of a sample of young rubella children with a suspected hearing loss are presented and compared with the findings from earlier studies. Such a comparison revealed that there is a remarkable similarity in the degree and configuration of the hearing losses resulting from different epidemics of maternal rubella. In most instances, a moderate to severe bilateral impairment with a relatively flat configuration was encountered. It is noted that most of the present sample were successfully evaluated initially at a very young age and that many of the children are now utilizing wearable amplification with apparently good results. Finally, it is stressed that at least one half of the present group of children with a history of maternal rubella are most appropriately categorized as partially hearing rather than as deaf.

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CROS Hearing Aids: A Breakthrough for the Unilaterally Deaf Patient and for Others with Special Hearing Problems

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For many years physicians and audiologists who have encountered patients with severe unilateral deafness have stressed that the hearing handicap is minimal. In counselling such patients, emphasis was placed on the fact that speech and language skills were unaffected, that the patient could still hear as well as ever on the telephone, and that most people who come in contact with him would not be aware of his hearing loss. Until recently, this course of action was most prudent inasmuch as there was neither treatment nor prosthesis available to ameliorate the hearing problems engendered by such a loss.

Within the past two years, however, a unique method of modifying a conventional ear level hearing aid has been developed which serves to reduce the special problems of the one-eared listener. The apparatus being referred to is known as a CROS (Contralateral Routing of Signals) hearing aid.[1, 2] With its appearance in the armamentarium of the audiologist, there has emerged the need for a reorientation among physicians. Now that help is available for the unilaterally deaf, it behooves the physician to recognize the hearing difficulties faced by his patient and to advise him accordingly.

It should be stressed at this point that a thorough otological examination should precede the selection of a hearing aid. On the one hand, cognizance must be taken of the possibility that the unilateral deafness may be surgically or medically reversible. But even more importantly, it may be necessary for the otologist to rule out the possibility of an acoustic tumor.

Hearing Problems of the Unilaterally Deaf

Among those listening problems most frequently mentioned by the unilaterally deaf patient are: 1) inability to hear speech from the side with the poor ear, 2) inability to hear speech efficiently in the presence of conflicting background noise, 3) inability to locate the source of environmental sounds, including speech, and 4) the sensation that the defective ear feels blocked. Within these general categories, there exists for certain individuals, highly specific impairment of hearing function which is usually dependent upon a variety of factors. Some of these factors include: occupation, cultural interests, sex, and personality.

In the United States, where automobile travel has assumed such importance, unilaterally deaf drivers and passengers are often made acutely aware of their losses. For the male, who usually drives when passengers are present, the loss of hearing in the right ear makes conversation difficult. By the same token, the female who accompanies a male driver has a communication problem if her left ear has the loss. In England, where drivers sit on the right side of the vehicle and passengers on the left, the reverse of the above is true.

The occupation of the patient may impose unusual listening requirements. For example, a male patient who was referred to our center with poor hearing in the left ear complained of a problem associated with driving. As mentioned previously, the male driver is most often troubled by poor hearing in the right ear, not the left. The explanation for this patient's difficulty became apparent when he reported that he was employed as an automobile driving instructor, whose work required him to sit with his left ear facing the student driver.

Another example, which serves to illustrate how highly specific certain occupational hearing needs may become, concerns a Catholic priest. This unilaterally deaf patient complained that his deafness decreased his efficiency in hearing Confession. According to custom, his parishioners approached the Confession Box from either the left or right sides.

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By opening one of two side windows, the average priest sitting inside the box is able to hear his parishioners regardless of which side they are on. However, seated within the close confines of the Confession Box, the unilaterally deaf priest was unable to maneuver his good ear to cover both windows. The ramifications of his unilateral deafness were humorously acknowledged by the priest who expressed the fear that if his secret leaked out, it might encourage the sinners to line up on his bad side.

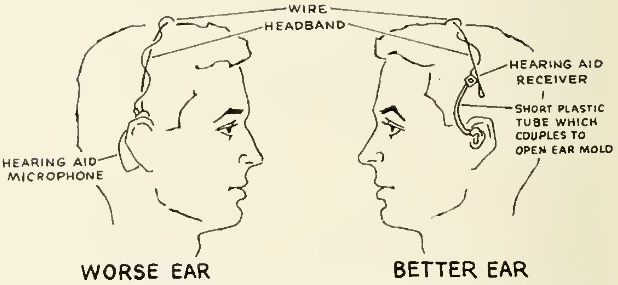
Musicians, whether amateur or professional, may also find unilateral deafness handicapping. The inability to monitor a musical instrument on the bad side may seriously interfere with the coordination among a group of players. One patient who was a piano player with a poor right ear, reported the need to twist into an awkward position in order to permit the left ear to listen to the notes played by the right hand. Another patient, who was a singer, stated that she found it necessary to sing out of the corner of her mouth toward her good ear in order to monitor her voice.

These examples which have been cited represent only a small portion of the occupations which penalize the unilaterally deaf patient. Other equally appropriate examples may be mentioned.

How the CROS Works

In each of the cases cited above, as well as in others not mentioned, the innovation that has proven successfull has been the CROS hearing aid. For those unfamiliar with the device, an explanation follows: The CROS hearing aid is made up of two basic parts — a standard ear level hearing aid, and an accessory attachment. The hearing aid itself may be either the type worn in eyeglasses or the kind that is worn behind the ear. Whichever type is used, it is necessary to place the hearing aid on the side of the head which has the poor ear. Sound originating on the side of the poor ear is picked up by the hearing aid microphone, amplified, and then sent to the opposite ear. The accessory attachment routes the sound from where it is picked up on the impaired side and directs it to the normal or near normal ear. A special open earmold, which is placed in the good ear, is an essential part of the CROS apparatus because it permits signals originating from the good ear side to enter the good ear canal without obstruction. At the same time, the good ear receives signals via either an electric or an acoustic coupler from the hearing aid on the poor ear.

A number of possibilities exist as to the way in which a CROS aid may be fitted. Selection of a suitable one may depend upon assessment of the specific needs and preferences of the patient. Figure 1 shows a schematic of the CROS mode using an electric coupling (wire) across the head. The schematic in Figure 2 shows the CROS mode using a behind-the-ear aid and an acoustic coupling (hollow plastic tubing) around the head. Figure 3 illustrates in schematic form, the CROS mode using a behind-the-ear aid and an acoustic coupling across the head. Figure 4 shows a schematic of an eyeglass CROS which makes use of an electric coupling around the head.



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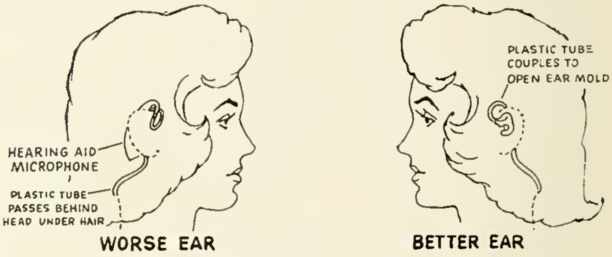
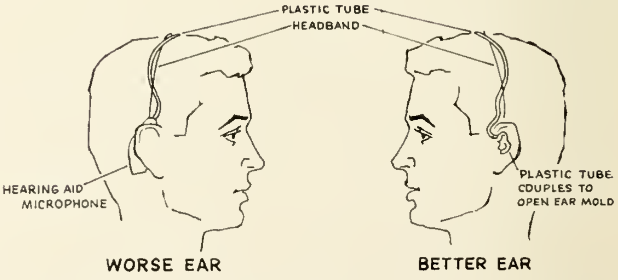

PLASTIC TUBE COUPLES TO OPEN EAR MOLD
HEARING AID MICROPHONE
PLASTIC TUBE PASSES BEHIND HEAD UNDER HAIR
WORSE EAR
BETTER EAR

2. Harford, E., and Dodds, E., The Clinical Application of



3. Harford, E., Bilateral CROS: Two Sided Listening With

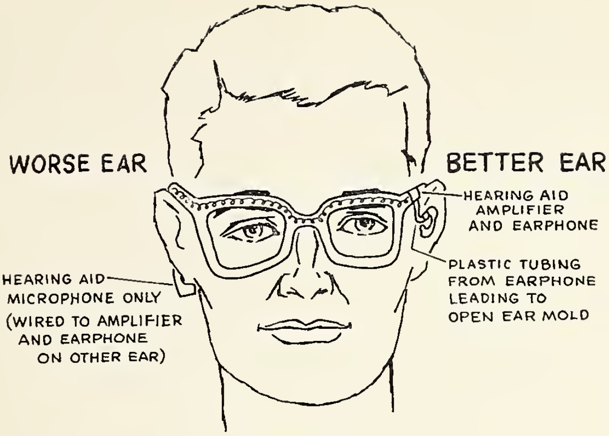

WORSE EAR
BETTER EAR
HEARING AID AMPLIFIER AND EARPHONE
PLASTIC TUBING FROM EARPHONE LEADING TO OPEN EAR MOLD
HEARING AID MICROPHONE ONLY (WIRED TO AMPLIFIER AND EARPHONE ON OTHER EAR)

Figure 4

In general, both the electric and the acoustic couplings terminating in an open ear mold will appreciably alter the amplifying characteristics of the hearing aid as it routes the signal to the contralateral ear. The addition of approximately 14 inches of tubing which is used in the acoustic coupling will also make an additional change in the amplifying characteristics of the hearing aid. The lengthened tubing will cause a slight overall reduction of output as well as a more sharply peaked frequency response.

Who May Benefit

Experience with CROS hearing aids at the New Haven Hearing and Speech Center has been limited to about a dozen cases, ranging in age from forty to seventy-three years. Despite this small number, the results have been so consistently successful in well selected cases that a great deal of enthusiasm has been generated. Unfortunately, a large number of patients who might benefit from a CROS hearing aid fitting are not being seen at the audiology centers. Most of these patients have been told at one time or another that there is nothing that can be done for them as far as a hearing aid is concerned.

For those who have not had firsthand experience with it, a CROS hearing aid fitting should be considered for the patient whose hearing shows the following:

Worse Ear	**Better Ear**
1. complete unilateral deafness	normal or near normal
2. moderate nerve deafness with poor speech discrimination	normal or near normal
3. high frequency loss with poor speech discrimination and eczema or other condition which makes a conventional earmold inadvisable	high frequency loss with poor speech discrimination and eczema or other condition which makes a conventional tional earmold inadvisable
4. high frequency loss with extremely poor speech discrimination	high frequency loss with poor speech discrimination
5. high frequency loss with an intolerance to the "sharpness of sound" of a hearing aid	high frequency loss with an intolerance to the "sharpness of sound" of a hearing aid
6. severe to profound conductive or mixed loss when surgery is contra-indicated and when the patient is opposed to the use of a body type hearing aid	normal or near normal

The patients who have been fitted with CROS hearing aids have experienced one or more of the following benefits: 1) "fullness of hearing", 2) ability to localize sound, 3) better hearing on the side with the bad ear, 4) the sensation of having the bad ear unstuffed, 5) the sensation that sounds are not as intolerably sharp as with a conventional hearing aid fitting, and 6) improved ability to function in the presence of conflicting background noise.

So far, the experience accumulated with CROS hearing aids at our center has been limited to adults. Whether this device has a successful application with children remains to be ascertained.

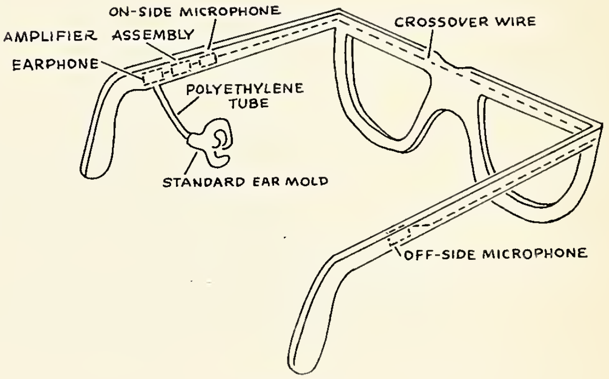


Figure 5

A recent outgrowth of the CROS is the Bilateral CROS, or BICROS.[3] Figure 5 shows a schematic of the BICROS in eyeglasses. The behind-the-ear BICROS hearing aid shown in Figure 6* is a prototype and is not generally available from hearing aid manufacturers as yet. As can be seen from Figures 5 and

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*courtesy Bernard Lipin, Beltone, New Haven

6, the BICROS fitting employs an ear level hearing aid and an additional microphone which is placed over the contralateral (unaidable) ear. The BICROS hearing aid is used when the patient has one unaidable ear and one that requires an aid. One successful BICROS hearing aid has been fitted at our center on a five year old boy but more experience is needed before generalizations can be made.

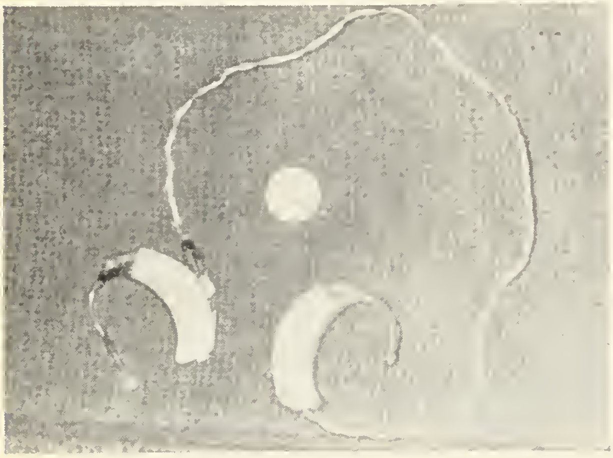

Figure 6. A photograph of a prototype of a behind-the-ear BICROS hearing aid. (The main body of the hearing aid is on the left; the additional microphone, housed in a dummy case, is on the right. This hearing aid may be worn either with or without the additional microphone.)

Summary

Until recently, physicians and audiologists have had little to offer the unilaterally deaf patient except the reassurance that the handicap was minimal. Nonetheless, the hearing problems encountered by this type of patient have been a real part of his life. With the advent of the CROS hearing aid, a breakthrough has occurred which has suddenly opened up the possibility of helping this large category of hearing impaired individuals. Now that help is available for the unilaterally deaf patient, there is a vital need for a re-orientation among both physicians and audiologists. After it has been determined that there is no medical reason to contraindicate its use, the audiologist should proceed to select a suitable CROS hearing aid. In carefully selected cases, a high degree of success may be expected.

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THE PRESIDENT'S PAGE

HAPPY Holy Days! And these Holy Days *are* happy. Thank goodness!

So often our impression of religion is oppressed by sin, guilt and gloom. Life wasn't meant to be that way. At least once a year the spirit of religion places emphasis on the cheerful side of life. Despite the harassment of preparations, frustrations and overwork this time of year, don't you almost hold your breath in an abstruse anticipation? And then a buoyancy and elation burst forth. There must be some reason.

It is interesting that the major religions of the West have chosen the darkest time of the year to bring a message of light. Both Christmas and Hanukkah come shortly after the winter solstice—just as the days slowly begin to lengthen.

An ultra-bright star brought three wise men to make their gifts to the newborn Jesus of Nazareth. He has since been called the "Great Healer", having ministered to the somatic and mental as well as to the spiritual needs of his people. His birthday, Christmas, is now a time for happiness, the lighting of lights, and the giving of gifts. A new life is born. Once again there is hope.

The simultaneous celebration of Hanukkah centers around the progressive kindling of lights for eight days. Gifts are given especially to the children. Some 2,132 years ago the Temple at Jerusalem was re-dedicated, having been profaned earlier by Antiochus Epiphanes in his effort to destroy the religion. Freedom to worship was thus restored. Again the feeling of hope, joy and a new beginning.

We physicians are most fortunate to be in a position where our pills and injections, our scalpels and sutures, our ointments and lenses and forceps can bring health, comfort, renewed life to our patients. Just as gratifying is the reaction to a little extra kindness, to some objective yet sympathetic understanding, to a bit of stern advice or an unmitigated order which also tells the patient how much we care. No matter what branch of medicine we practice, we can lift up the spirit even if we cannot always cure the disease.

The officers and your wonderful staff at 160 St. Ronan Street join me in wishing each one of you and your families great happiness at this season—and to you the greater joy of bringing the light of Christmas and Hanukkah to each of your patients throughout the year.

E. TREMAIN BRADLEY, M.D.

THIRD CONFERENCE OF COUNTY MEDICAL ASSOCIATION OFFICERS

Thursday, September 14, 1967, New Haven, Connecticut

Theme: The Title XIX Program of Medical Assistance

THE PHYSICIAN, THE GOVERNMENT, THE PATIENT

E. Tremain Bradley, M.D., President, CSMS

Government has moved into a very popular field —medicine. This invasion should be of concern to every voter and all his dependents. The administration of medical care for *all* our citizens would certainly be "big business", and offer widespread opportunities for political patronage in the hundred-and-one bureaucracies that would be set up to keep everyone in line. The government is powerful, all right, and some are saying that since "socialism is inevitable, why don't we all sit back and enjoy it?"

In commenting on the actions of the 1967 General Assembly, Commissioner Shapiro has emphasized that effort, persistence and integrity *can* accomplish great things. We got a Title XIX program—and one with great potential for good. We must all help to make it work so that the potential is realized. It being our responsibility to give quality care to *all* of our patients, we must see to it that we have a Medicaid plan within which we can exercise our best medical judgment as to diagnosis and treatment, and that patients are free to choose the providers of their health services from among those available and qualified in their home communities—just as non-assistance patients are. We believe that these protections are the keystones of the American system of private medicine, and that they must be preserved.

The Physician, the Government, the Patient: It is vital that all people have good medical care available to them—also food, clothing, housing and other necessities of life. Federal and state governments are joining forces to finance medical care for the indigent and for others who are bordering on indigency. Health care providers will be furnishing the medical care, but taxpayers will be footing the bills. Hence, it will be understandable if the public insists that the total cost be kept within reasonable bounds. To the extent that we can help to control those costs, we have an obligation to do so. We must be willing to work *with* government in implementing all aspects of Medical Assistance. We must not consent, however, to work *for* government, since, thus far, the government does not own us or our services.

Title XIX patients, too, will have a responsibility to make the program work both effectively and economically. They must be educated to avoid wasting the doctor's time; to not ask for unnecessary medical goods and services; to not question the doctor's judgment about hospitalization, whether for admission or discharge. In a word, patients must cooperate to assure that neither under-utilization nor over-utilization become characteristics of any part of this comprehensive program.

At all times the competent physician must try to deliver care of the highest quality, but, at the same time, exercise prudency in ordering tests and treatments, in prescribing exotic drugs when more commonplace ones would do just as well, and in limiting hospital stays to not a day more than is medically required. Fees should be maintained at usual and customary levels, without escalation, and without regard to whether the patient is self-paying, covered by insurance, or entitled to Medicaid benefits. We should be willing—even anxious—to have our charges reviewed by our peers in the event that they are questioned.

Our State Medical Society must try to inform its members about these responsibilities, and to try to keep them informed. Medicine at all levels must keep its houses in order by preventing or correcting improper practices, by promoting self-regulation among physicians in the matter of charges and utilization of services, and by imposing appropriate discipline when members are proven to be errant.

The federal government played a very cagey game in the enactment of Title XIX as a hidden rider to Medicare (Title XVIII). Medicaid was conceived behind drawn curtains and was railroaded through without public hearings. It is doubtful that more than a few representatives and senators who voted for the measure had ever read the bill; most now admit that they didn't understand it when the vote was taken. But, despite all that, we have a Medicaid Law and it isn't by any means all bad. It provides us with the opportunity to do away with "second-class citizenship" in medical care, and to break up the "ghetto" patterns of health services for the less fortunate.

Title XIX assures that its beneficiaries will have free choice of physicians and institutional facilities to the same extent enjoyed by others in any given community. It assures continuity of care under one's own doctor, whether rendered in the office, the home or the hospital. And it assures that "reasonable" costs or charges will be paid to the providers of health services, and elimination of the substandard payment schedules of the past.

Under Connecticut's Medicaid Program (Public Act 548), physicians will be paid on the basis of their "usual and customary charges" on and after March 1, 1968 and until March 1, 1969. If proven successful, recommendations will be made to the 1969 General Assembly that it be continued in the future. While some may refer to this as a "trial" period, I know that Commissioner Shapiro shares our view that it is really much more of a "pilot program"—one which, with the full cooperation of all concerned, can serve as a model for the future. We know that most doctors are responsible people; their past record of medical philanthropy is proof of that. They have already been demonstrating their ability to make "usual and customary" work for well over a year now, as is attested to by favorable experience with Medicare B.

To make the transition from a fixed fee schedule to usual and customary charges may prove to be somewhat more difficult for the State Welfare Department, which has had no previous experience with this newer method of payment. You will recall that Connecticut General, despite its vast experience and fund of information about regional variations in normal fee patterns, was not able to get Medicare B running smoothly for at least eight months. I must state here for the record that to the Title XIX Professional Advisory Committee, which met for the first time on September 1, it appears that for the Welfare Department to obtain adequately trained personnel to administer a usual and customary method by March 1, 1968 will constitute an almost insuperable task. This factor, coupled with a lack of experience and necessary data, makes the PAC doubtful that an operation comparable in efficiency to Medicare B can be established by the Department in less than eight or ten months—possibly leaving only two or three months of the pilot program to prove its true merit. This possibility is of considerable proper concern to physicians, since the Professional Advisory Committee and the Commissioners of Welfare, Finance and Control must base their recommendation to the Assembly for continuance (or discontinuance) of the method beyond March 1, 1969 on how well it has functioned, in addition to how much it has cost. I know that Commissioner Shapiro is cognizant of *his* responsibility to give the program a full twelve months of fair trial, and it is this which is prompting him to keep an open mind on the question of "farming out" its administration to an intermediary of established experience.

The Council is seeking suggested nominees from the county medical associations, sections and specialty groups for service with the Title XIX Medical Advisory Committee, and will shortly submit a list of the names of qualified physicians to the Commissioner for his appointment to the Committee. The MAC, with a majority of its members nominated by the Society, will assist the Commissioner in reviewing disputed or questionable claims for payment. Being physicians, rather than insurance actuaries, their principal assistance will be rendered in cases where medical necessity and proper utilization have to be determined. Their knowledge of the prevailing levels of "usual and customary charges" in various parts of the State will be somewhat limited, which, again, points up the importance of having experienced personnel handling that part of the program.

The Medicaid Law requires that at least 60% of all physicians participate in the program, including equivalent numbers in each specialty, and that the rates of payment and other conditions shall be such as to assure this degree of participation. If a state plan falls short of achieving this desired goal, its Medical Assistance program may be in jeopardy and it is apt to lose out on Federal matching funds. I feel sure that Commissioner Shapiro will continue to exercise the fine spirit of cooperation that he demonstrated last spring when we appeared together before the General Assembly in support of the Title XIX bills. On our part, I am sure that he can count on every member of the Society to use restraint and good judgment in rendering care to Medicaid beneficiaries and in making claims for payment for their services.

PLANS AND TIME-TABLE FOR IMPLEMENTATION OF TITLE XIX PROGRAM

Bernard Shapiro, Commissioner, State Department of Welfare

It is with considerable pride and pleasure that I discuss with you today our Title XIX Program. Connecticut's Program didn't just happen. It developed out of the needs of people and represents the thinking, planning and dedication of persons who were and are concerned with the welfare and health needs of those in the State who need financial assistance with their medical expenses. Without the support and cooperation of many other groups such as the professional groups, health and welfare agencies and, last but not least, interested citizens, we would not today be administering our present comprehensive medical assistance program.

I do not want to give you the impression that we are complacent about our achievements, but we can be honest enough with ourselves to recognize them and to pledge our concerted efforts in the attainment of the ultimate goal, namely the provision of adequate and quality medical services to all medically needy persons in Connecticut. Let me describe briefly to you our Medical Assistance Program as it started in July 1, 1966, the changes that have taken place to date and the changes which will become effective within the year.

Plans in Connecticut For Implementing Title XIX — Medical Assistance Program

Public Act 357, passed by the General Assembly of the State of Connecticut June 24, 1965, authorized the State Welfare Commissioner to take advantage of the Medical Assistance Programs provided in Title XIX except with respect to individuals 65 years of age or older who were in institutions for tuberculosis or mental diseases. In accordance with the requirements of Public Law 89-97 and in keeping with the Connecticut State Law enacted by the General Assembly, the Governor designated the State Welfare Department as the state agency to administer and/or supervise the administration of the Connecticut State Plan for Medical Assistance under Title XIX of the Social Security Amendments of 1965.

Under our Program, medical assistance is made available to the following groups:

1. Beneficiaries of money payments under the Old Age Assistance, Aid to the Blind, Aid to the Disabled and Aid to Families with Dependent Children programs.
2. Children committed to the State Welfare Commissioner under the Child Welfare program.
3. Children under 21 who are members of a family receiving basic maintenance under the General Assistance programs.
4. Medically needy persons who are categorically related, i.e., persons who meet all the eligibility requirements of OAA, AB, AD or AFDC, except that income and resources are sufficient to meet basic maintenance needs.
5. Medically needy children under 21 not included in any welfare maintenance program. This includes the following groups:
   - (a) Medically needy children under 21 years of age who are members of an AFDC family but ineligible for AFDC maintenance.
   - (b) Medically needy children under 21 receiving Protective Services, Protective Supervision, Services under the Unmarried Mother's program or who are non-committed children under the Child Welfare program.
   - (c) Medically needy children under 21 who are under the guardianship or custody of a private agency and for whom the private agency is assuming financial responsibility in whole or in part.
   - (d) Other medically needy children under 21 years of age in the Community.

The income and resources of persons or families which were protected for basic maintenance needs followed the same pattern as the State had for its Medical Assistance for the Aged Program.

	*Income**	*Assets*	*Insurance* (Family Maximum)
Single Person	$2,100	$ 900	$500
Couple (1 Adult—1 Child)	$3,200	$1,300	
Each Additional Member of Family	$ 300	$ 100	

*Plus—*Health Insurance Premiums*
$150.00 — for single person
$250.00 — for couple
$350.00 — for family of 3 or more

The scope of medical coverage is comprehensive, equal in amount and duration and the same as we had in all our public assistance programs prior to July 1, 1966 with one exception. One additional item was included in this comprehensive program, namely; physician's services in a general hospital.

Our Medical Assistance program was broadened and strengthened by the General Assembly in 1967 with legislation effecting the following changes:

Income and Resources

The annual income limits increased as of July 1, 1967 so that a family of four with a gross annual income of $4,400 a year is eligible to have its medical costs paid by the Department. Previously, $3,800 a year was the income level for eligibility for a family of four. The specific income change is an increase from $300 to $600 a year for each dependent (in addition to) over and above the initial two persons. The personal property limits were raised from $900 to $1,400 for one person; $1,400 to $1,900 for two persons; and $100 to $200 for each additional dependent. It is estimated that approximately 5,000 additional families will become eligible for payment of needed medical services in the course of a year.

Payment and Care for Patients 65 Years of Age and Over in Public Mental and Tuberculosis Institutions

In February, 1967, the program was extended to needy patients 65 years of age and over in mental and tuberculosis institutions. Approximately 1300 patients have been found eligible for the program and the cost of care is being paid by the Welfare Department. This has resulted in an increased revenue in Federal matching funds at 50% of Welfare expenditures. The current estimate is that the annual state revenue derived from this source will amount to $3,500,000.

Customary and Usual Fees To Physicians

As I view it in the field of health care, perhaps one of the most significant areas of outstanding service and accomplishment made possible through the efforts of the State Medical Society and the Title XIX Advisory Committee was the passage of legislation (P.A. No. 548) in regard to the implementation of customary and usual fees. With the passage of this Public Act, payment to physicians for a one year period March 1, 1968 to March 1, 1969 will be based on customary and usual charges prevailing in the locality. Dentists and other practitioners of the healing arts will have a revised fee schedule beginning October 1, 1967, based on moderate and reasonable rates prevailing in their respective communities. This is indeed a big step forward even though the usual and customary fees are limited to physicians and only during the one year test period. It is apparent that the Legislature, when it evaluates the program in 1969, will be interested in costs as well as quality of care. In fact, the concept of customary and usual fees cannot be extended beyond the test period, until the Legislature makes an evaluation, since this was the purpose of the legislation. During this period, excessive fee charging and over-utilization will be closely watched.

The Medical Advisory Committee will assist the Welfare Commissioner in reviewing all claims for payment in which doubt or dispute is raised by any party to the medical assistance program and by making recommendations to the Welfare Commissioner concerning such claims. It can be said that the work of this committee, which has just begun, has no limits in sight if we can use as a yardstick its accomplishment in so short a period of its existence.

I believe you will be interested in the number of cases served by the Title XIX Program for the first complete year—July 1, 1966 thru June 30, 1967:

	OAA	*AFDC*	*AB*	*AD*	*TOTAL*
Active Cases—7/1/66	5,598	12,952	291	9,456	28,297
Cases Added— 7/1/66 thru 6/30/67	3,382	6,971	48	1,799	12,200
TOTAL Active Cases 7/1/66—6/30/67	8,980	19,923	339	11,255	40,497

Total CASES Active 7/1/66 to 6/30/67—By Program:

C.W.	*O.A.A.*	*A.F.D.C.*	*A.B.*	*A.D.*	*M.A.*	*TOTAL*
8,000	8,980	19,923	39	11,255	24,401	72,598 cases

3 additional persons in AFDC Family — 60,000 persons
132,598 "
Liberalization by Legislation — 18,000 "
150,000 "
(Roughly 5% of Population)

I believe you will be interested in the current legislation with regard to Title XIX that is pending before the Congress. The Committee, chaired by Representative Wilbur Mills, noted that some 30 states now have Title XIX medical assistance programs in operation, with eight more states soon to be added. It expresses concern, however, that the plans in a few states go well beyond what Congress had in mind when the program was authorized.

The Committee reports that it never intended that Federal matching under Title XIX would be made for the medical costs of a considerable portion of the adult working population of moderate income.

The bill therefore would establish maximum income levels for payment of medical assistance for the medically needy. These maximums would not be set in dollar amounts, but would be in relation to the highest amount that would ordinarily be paid to a family of the same size receiving money payments through AFDC, and having no other income. For states already having a Title XIX program in operation the federal matching ceiling for the medically needy, effective July 1, 1968, would be an income level of 150 percent of the AFDC money payment. On January 1, 1969 the ceiling would be reduced to 140 percent, and on January 1, 1970 it would be permanently set at 133-1/3 percent.

As you can see, the House Bill this year contains a severe limitation on Federal participation—a limitation which will affect the programs in operation in 14 states. The fourteen states affected by the House Amendment are California, Connecticut, Delaware, Illinois, Iowa, Kentucky, Maryland, Michigan, Nebraska, New York, Oklahoma, Pennsylvania, Rhode Island, and Wisconsin.

For Connecticut this may mean that the 2,100 dollar income for single persons may have to be reduced by $200. The $3,200 current State Plan Income Allowance for two (2) persons may have to be reduced by $600.

The Department has vigorously protested this provision in the House Bill and we urge you, as a Medical Society, to do the same by communicating with Senator Russell Long, the Chairman of the Finance Committee, and Senator Abraham Ribicoff who is a member of the Committee.

The Johnson Administration has recommended that to remedy this discrepancy and to establish a reasonable relationship between need for cash assistance and medical indigence, that the President's proposal to limit eligibility for medical assistance to 150% of the needs standard for cash assistance be adopted.

Laboratory Medicine

Serum Alkaline Phosphatase

Although it has been known for a number of years that the alkaline phosphatase of serum may originate from different organs, until recently there has been no practical method for recognizing the site of origin through examination of the blood. Recently J. M. Yong of St. George's Hospital Medical School in London has developed a useful method, although one which must still be considered as too specialized for the ordinary clinical laboratory. His method[1] relies on agar gel electrophoresis using extremely cold buffer, followed by a staining method with a hydrolyzed naphthol substrate. The major contributions of this method are in establishing the origin of alkaline phosphatase enzyme in categories of disease; in individual patients the origin is usually clear when the clinical setting is studied. The electrophoresis sharply separates liver, bone, intestinal and placental enzyme when combined with study of heat stability and L-phenyl alanine inhibition.

Yong's conclusions may be summarized as follows:

1. Normal adult serum contains predominantly liver-type enzyme, a small but variable amount of intestinal enzyme, little or no bone enzymes.

2. In children there is liver enzyme plus bone enzyme, the amount of the bone type gradually falling with age.

3. In pregnancy the rise in serum alkaline phosphatase is due to placental enzyme.

4. The liver enzyme can be of 2 types, one of bile duct epithelium and the other of endothelial origin. In obstruction the bile duct type escapes into the blood, in hepatocellular disease it is the endothelial type which rises. Infants, who form little of either type, may have no alkaline phosphatase elevation even with complete bile duct atresia.

Roy N. Barnett, MD

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1. Yong, J. M. Origins of serum alkaline phosphatase. J. Clin. Path. *20* 647-653, July 1967.

Whither Usual And Customary Charges?

(On October 18, 1967, the Council voted to remind the membership of the Society's policy on "usual and customary charges", of the reasons behind this policy, and of the long-range benefits that its advancement offers.)

Since 1963, it has been the policy of the Connecticut State Medical Society that the preferred method of payment for physicians' services by all third party payors is that of "usual and customary charges". Taking into account the established fact that fee patterns vary throughout the country, and even within state boundaries, this newer method of third party payment requires: that (a) in submitting claims for payment, each physician will bill only for the amount that he charges the majority of his private patients (his *usual charge*) for the service rendered; that (b) the usual charge fall within the *customary* level of charges made in his community area by physicians of similar qualifications for a similar service; and that (c) if the charge is in conformance with the two previously stated criteria, it will be honored by the payor as being *reasonable*. A most important negative characteristic of the method is that *no schedule* is used to measure the reasonableness of a fee-for-service.

While the Society does not, in any sense, claim full credit for the increasing trend of third party payors, both private and public, to adopt the usual and customary charge concept in all their policies and programs, its efforts have contributed substantially to its use in the following plans in Connecticut: Medicare B, Military Dependents Medical Care, and Title XIX Medicaid (beginning March 1, 1968). To be sure, these three are government-financed programs, in part or in full, but reports are coming in from all over the United States that privately operated prepayment and insurance plans are making the transition from schedule to non-schedule payments under their *basic* contracts as well as major medical.

Perhaps the strongest arguments against a continuation of the fixed-fee approach are that: (a) fixed payments, however generous, do not accommodate the charges of physicians which may be higher *or* lower than the uniform amounts allowed, and that they are slow to reflect changes in the cost of living: (b) they take away from the individual doctor the right to assess the value of his own services and the initiative to deal person-to-person with his patients; and (c), their acceptance by physicians at local or state level may help to bring about realization of the dream of large segments of organized labor and a number of social planners that fees will someday be uniform *nationally* —exactly the same in Los Angeles, California and Hickory Hollow, North Carolina.

A little extra thought should be given to the last of these three arguments. There is no question that a national fee schedule would greatly simplify labor-management negotiations on employee health benefits, particularly in cases where management's interests cross state lines or even lie on opposite shores of the land. But, on the other hand, it is certain that such a convenience to these organized, so-called "consumers" of medical care services would eliminate all competition among hundreds of existing prepayment and insuring agencies, which competition has stimulated so much productive growth and expansion in the health insurance field. And then what? Why, what could be simpler or more logical than that the Federal government should step in and "coordinate" the entire private insurance sector under its own supervision, thereby eliminating completely the need for the existence of separate plans in the first place—to develop and administer programs at local level to meet local requirements at rates which reflect local economic conditions.

Widespread physician support of the usual and customary charge method will help to forestall this happening. Such support may prove to be the *only* way to try to achieve that end. The Society recommends that its members consider the merits of giving the new method their wholehearted backing, and of communicating to all third party payors in the State with whom they do business their favor for its use.

W.R.R.

FROM THE GENERAL MANAGER'S OFFICE

WILLIAM R. RICHARDS, M.D., *General Manager*
160 St. Ronan Street, New Haven, Conn.
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Peter F. Villano
Director of Public Relations

Josephine P. Lindquist
Assistant to General Manager

SUMMARY OF ACTIONS COUNCIL MEETING

Wednesday, October 18, 1967

I. Attendance

Present in addition to the Chairman, Dr. Stevens J. Martin were: Drs. Bradley, Grendon, Polivy, M. Caplan, Fabro, Hess, Rogol, Cramer, Abbot, Spitz, Hastings, Shepard, Ayres, Jacobson, Jr., Grant, Petrie, Pelz, Wilson, Palomba, Roch and Granoff.

Also present were: Mrs. Lindquist, Mr. Villano, Mr. Norbeck (AMA) and Dr. Richards. Absent were: Drs. Gardner, Egan, Johnson and Nolan.

Preliminary

Before starting the business meeting, the Chairman introduced Morris A. Granoff, New Haven, who has been appointed by the New Haven Association as Associate Councilor. Note was made that Stewart J. Petrie, Derby, has been appointed NHCMA Councilor to succeed Frank K. Abbot, Waterbury, who resigned to become Vice-Speaker of the House of Delegates.

The Chairman also drew the attention of the Council members to the handsome scroll, hanging in the Barker-Weld Room, which was accepted by the Society's President from the President of the Hartford County Medical Association on September 27, 1967. The scroll was presented to the Society by the Hartford Association in commemoration of the Society's 175th anniversary of its founding and in recognition of its contributions to Medicine in the state. It was VOTED to request the General Manager to convey to the President and members of HCMA the sincere thanks of the Council for this expression of esteem for the Society's efforts during the period 1792-1967.

II. Routine Business

Life Memberships

It was VOTED to approve applications for Life Membership received from the following eligible Active Members:

Henry Caplan, Yalesville, (NHCMA)—1968
Henry P. Talbot, Hartford, (HCMA)—1967
George C. Wilson, Norwich, (NLCMA)—1968

Committee Resignations

(a) *Committee To Study Perinatal Morbidity and Mortality:* It was VOTED to accept, with regret, the resignation of David F. Conway, New Haven, as a member of this Committee.

(b) *Committee on Program of Scientific Assembly:* It was VOTED *not* to accept the resignation of David Babbott, Hartford (now of the Vermont Medical School), as Chairman and as a member of this Committee. Dr. Babbott informed the Council that, having moved out-of-state, he would be unable to give in-person attention to his duties as Chairman, but that he would very much like to participate in planning and conducting the program to the fullest extent possible. William F. Eckhardt, New Canaan, who will become Chairman of the Committee for the 1969 Scientific Assembly is agreeable to serving as Acting Chairman for the balance of the current year, with Dr. Babbott continuing on as official Chairman.

Date Of Next Meeting

The next meeting of the Council will be held on Thursday, November 16, 1967.

III. Old, New and Special Business

Report—Committee On Third Party Payments

(a) As recommended by the Committee, it was VOTED to adopt a policy statement which reads as follows: "It should be a guideline in the functioning of Review Committees that third party payors be asked to advise the patient (policyholder) only of his allowable payment, and that further questions regarding charges be a matter for discussion between the patient and the physician." Copies of this statement are to be sent to the Health Insurance Council and other appropriate agencies.

(b) It was VOTED to receive as information notice: that the project to update the Relative Value Study has been set in motion; and that a meeting has been scheduled with the chairmen of four of the Society's sections to discuss the relative values of services provided by physicians in extended-care facilities and appropriate utilization of same.

Report—CSMS Representative To P.L. 89-749 Program

Orvan W. Hess, New Haven, CSMS representative on the Advisory Committee to the "Comprehensive Health Planning and Public Health Services" program in Connecticut, reported that progress has been made toward setting up the administrative mechanisms to start implementing the program, but that, thus far, no definitive studies are under way.

COMPAC

(a) It was VOTED to receive, as information, a copy of the minutes of the August 22, 1967 meeting of the Board of Directors of COMPAC.

(b) It was VOTED to accept a report of the Ad Hoc Committee on CSMS-COMPAC Liaison presented by the Committee Chairman, Frank K. Abbot. and to approve its recommendations as follows:

(1) That the officers of the Connecticut State Medical Society publicly promote COMPAC membership to CSMS members.

(2) That the agenda of the House of Delegates of the Connecticut State Medical Society regularly include a formal report from COMPAC, both at the annual and semi-annual meetings.

(3) That the Council of the Connecticut State Medical Society urge similar promotion of COMPAC by the officers of the component county medical associations, and similar inclusion of formal reports from COMPAC at their associations' annual and semi-annual meetings.

Report—Connecticut Society Of Pathologists

It was VOTED to accept a report filed by the CSP on its "evaluation of . . . out-of-state laboratory operations, with particular reference to the quality of their work and the charges attendant thereto (as compared with Connecticut standards and charge levels)", and to approve its recommendations as follows:

(a) That the Connecticut State Medical Society not accept as exhibitors or advertisers any laboratory not subject to supervision by the Connecticut State Health Department, or which offers contract practice arrangements.

(b) That the Connecticut State Medical Society condemn any "contract practice" (for laboratory services) of the type discussed as unethical, and not in accord with the principles (of ethics) which guide members of the Society. *N.B.:* A further report on the "ethics" of these arrangements is being awaited from the Council's Committee on Preliminary Study of Censorship Questions.

Pursuant to the acceptance of this report, and approval of its recommendations, it was VOTED to request the Committee on Public Health to undertake a study of the costs of laboratory services and testing in Connecticut and to what extent laboratories (hospital and otherwise) within the state contract (sub-contract) with out-of-state laboratories for services and tests; to seek to determine, if asked, the accuracy of tests and services performed by out-of-state laboratories; and to report to the Council on these matters.

Communication—Hartford County Medical Association

Having received from the Board of Directors of HCMA a series of suggested changes in the wording of two documents sent to all component county medical associations earlier this year ("Proposed Rules Governing Disciplinary Proceedings" and "Model Section on Ethics and Discipline; a Guide for the Constitutions of County Medical Associations"), it was VOTED to refer these suggestions for change to the Committee on Preliminary Study of Censorship Questions (which authored the original documents) for further study and report, and that other counties be invited to submit their recommendations regarding these Guidelines.

Having received and reviewed a communication from the Board of Directors of HCMA, concerning proposed amendments to the amendments (re establishing a "Judicial Committee") now lying on the table of the House of Delegates, it was VOTED to bring the HCMA amendments before the House of Delegates on December 13, 1967 by instituting the following procedures:

(a) The General Manager will communicate with the other component associations, asking their governing bodies to submit (on or before November 15) to the GM's office any amendments to the amendments on the table which they may wish to propose.

(b) The HCMA amendments, and any others which may be received, will be reproduced and distributed to the Presidents of the component associations and to all members of the House of Delegates at least ten days prior to the meeting of the House on December 13, along with copies of the amendments that are lying on the table.

(c) The Speaker of the House will be asked to appoint a Reference Committee at least two weeks prior to the meeting of the House of Delegates, such Committee to limit its hearing to this single item of business (amendments to the amendments re establishing a Judicial Committee), and each member of the Reference Committee is to receive all materials relating to the subject matter in advance for prior study.

(d) The Reference Committee appointed for this single purpose will hold its hearing in the forenoon of December 13 (probably starting at 11:00 A.M.), and will be expected to have a report prepared in time for submission to the House during the afternoon session (starting at 2:00 P.M.). Any CSMS member may appear and testify at the hearing.

(e) At the time of presentation of the report of the Reference Committee to the House, additional debate on all aspects of the amendments will be permitted from the floor, but it is hoped that Delegates and members-at-large will have made their points, pro or con, at the Reference Committee hearing and will not infringe on the time of the House by making the same points from the floor.

Reports—Council's Fiscal Advisory Committee

It was VOTED to approve recommendations of the Fiscal Advisory Committee as follows:

(1) That the Council approve the proposal of the Committee on Medicine and Religion to plan and hold an M and R program ("The Doctor's Dilemma re Contraception, Abortion and the Use of Psychedelic Drugs") at the Hartford Hilton, Hartford, at 8:00 P.M. on Tuesday, April 30, 1968 (the first day of the Annual Meeting), and to authorize the Committee to spend up to $750 out of general funds for the purpose of arranging and holding such program.

(2) That the Council authorize reimbursement of a member of the Committee on Public Health in the amount of $160.80, such reimbursement to cover part of the costs incurred by the member in attending the meeting of the American Public Health Association, Miami, Florida, October 22-27, 1967. It is understood that the member, acting as a CSMS representative, will file an informative report on the proceedings of the meeting for distribution to the Council, the Committee on Public Health, and others who may be interested.

(3) That the sum of up to $1195 be made available to the Committee on Postgraduate Education during the period November 1, 1967-June 30, 1968, such funds ($235) to be used for the purpose of soliciting and collating the places, dates and contents of educational programs throughout the State which are available to members of the Society and up to $960 to cover the costs of publishing this information in the Journal. The administration of the funds (Journal costs, printing and postage, personal services, etc.) will be the responsibility of the General Manager's office. For the time being, the tasks of obtaining, coordinating and publishing the information on these educational programs will be the responsibility of the Public Relations Department. Later on, it is possible that additional clerical help may have to be engaged.

(4) That the Council approve an educational grant to COMPAC for 1968 in the amount of $7,500; that this allocation appear in the budget for 1968; that the Council recommend approval of this grant to the House of Delegates on December 13, 1967; and that the opinion of the governing boards and/or membership of the component county medical associations on making the grant be sought in writing for transmittal to the House of Delegates on December 13, 1967, along with the budget and the recommendation of the Council.

(5) That the Council authorize the Chairman, in consultation with the President and the General Manager, to designate two qualified members of the Society to serve as CSMS representatives to an AMA Planning Conference on Health Care for the Poor, Chicago, December 15-16, 1967, and to authorize reimbursement of the members designated for usual expenses incurred by their attendance at the Planning Conference at the rate of up to $250 per representative.

(6) That the Council approve the publishing of an AMPAC-COMPAC advertisement in the Journal as a "filler", as frequently as possible and without charge to COMPAC.

Report—International Conference On Abortion

It was VOTED to accept a report on the proceedings of this Conference (Washington, D.C., September 6-8, 1967) filed by the President, E. Tremain Bradley.

Pursuant to the report, it was VOTED to adopt a motion as follows:

> That the Chairman of the Council appoint an Ad Hoc Committee to Study the Problems of Abortion, and request the Ad Hoc Committee to report the results of its study to the Council within a reasonable time. It was the sense of the Council that the Committee explore the subject of abortion in its broadest aspects, with particular emphasis on the various medical, social and economic forces which contribute to abortion; that the membership of the Committee include informed individual physicians and members of pertinent CSMS committees (Medicine and Religion, Public Health, Maternal Morbidity and

Mortality, Perinatal Morbidity and Mortality, etc.); and that the Committee be authorized to meet with other informed persons and use all avaliable resources in its study.

Report—Liaison With State Dental Association

It was VOTED to accept the report of the President, E. Tremain Bradley, on his discussion of this subject with the President of the Connecticut State Dental Association, and to approve the following recommendation:

> That an invitation be extended to the Connecticut State Dental Association to have two or three CSDA representatives join the Council at its meetings, at least once within every six months period, for the purpose of presenting and discussing matters of mutual interest to the organizations and their members.

Report—Meeting Of Organization Of State Medical Association Presidents

It was voted to accept, with commendation, a report on the proceedings of this meeting (Chicago, August 24-25, 1967) led by the President, E. Tremain Bradley.

Pursuant to the report, it was VOTED to approve a series of recommendations as follows:

(1) That the Council of the Connecticut State Medical Society strongly condemn any movement to discontinue hospital-based, diploma schools of nursing and licensed practical nursing, and that the Connecticut Nurses Association, the Connecticut League for Nursing, the Connecticut Hospital Association be apprised of this action; further, that the action be widely publicized to the communications media.

(2) That the Chairman of the Council appoint an Ad Hoc Committee on Health Care of the Poor to study the problems in Connecticut which may result in inferior and/or inadequate medical care for the indigent and semi-indigent and report its findings and recommendations to the Council. It was further VOTED that the Chairman, in appointing the Committee, should include as members and co-chairmen the two CSMS representatives who are selected to attend the AMA Planning Conference on Health Care for the Poor, Chicago, December 15-16, 1967.

Report—Committee On State Legislation

It was VOTED to receive as information, and with thanks, a report of Isadore H. Friedberg, Chairman of this Committee, titled: Proposed Protocol on Long-Range Legislative Activities for CSMS.

Supplementary Report—Committee On State Legislation

It was VOTED to approve recommendations of the Committee, with minor amendments, as follows:

(1) That the Society's staff explore ways and means of obtaining and processing bills placed in the General Assembly's hopper more expeditiously, so that the Committee may have as much information about bills of interest to the Society available for study at the earliest possible time.

(2) That the Committee be authorized to reexamine and define the role to be played by the Society's legislative agent in future years, and to make specific recommendations concerning same to the next meeting of the Council (November 16, 1967).

(3) That the Committee, with the assistance of the Society's staff, be authorized to develop methods to assure a more effective flow of information from the Council to the Committee and return on a continuing basis, and that the Chairman of the Committee be requested to attend, and to report to, each meeting of the Council two months prior to, and during, each session of the General Assembly.

(4) That well in advance of each session of the General Assembly the Council assign responsibility to selected members of the Society (other than members of the Committee and staff) to appear at legislative hearings on "key" bills (those initiated by the Society or in which the Society has special interest).

(5) That the Council express its desire that the Committee be "active" in entering into legislative areas for the common good (gathering, studying and evaluating health problems with a view to having the Society introduce bills, when appropriate).

It was VOTED to table action on one recommendation of the Committee which proposed to define areas in which the Committee could act autonomously and those in which prior approval of the Council and/or House of Delegates should be obtained before legislative action is undertaken.

It was further VOTED to adopt a motion (recommendation) *not* submitted by the Committee as follows:

> That the Chairmen of all standing and special committees of the Society seek contact relationships with the Chairmen of pertinent committees of the General Assembly to explore matters of mutual interest in the field of health and medical care legislation, and that the Chairman of the Committee on State Legislation be responsible

If it doesn't work in a week, forget it.

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently. Large doses of Butazolidin alka are contraindicated in glaucoma.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make regular blood counts. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The most common are nausea, edema and drug rash. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Mild drug rashes frequently subside with reduction of dosage. However, rash accompanied by fever or other systemic reactions usually requires withholding medication. Purpuric rash has also been reported. Agranulocytosis, ex-

In rheumatoid arthritis, Butazolidin alka needs only a week's trial. If it doesn't work in a week, forget it.

A short trial period may spare patients weeks of discomfort. That's one reason why Butazolidin alka seems a good choice when aspirin fails.

It's not for every patient. Check carefully the Contraindications, Warning, and Precautions shown below.

And adverse reactions may occur. The most common are nausea, edema and rash. Rarely, agranulocytosis has been reported. All adverse reactions are listed below, too.

You'll know quickly if it works.
And most of the time, it will.

foliative dermatitis, Stevens-Johnson syndrome, or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Rheumatoid Arthritis: Initial: 3 to 6 capsules or tablets daily in 3 or 4 equal doses. Trial period: 1 week. Maintenance dosage should not exceed 4 capsules or tablets daily; response is often achieved with 1 or 2 capsules or tablets daily.
6509-V(B)R2
For complete details, please see full prescribing information.

Butazolidin® alka

Capsules: phenylbutazone, 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate, 150 mg.; homatropine methylbromide, 1.25 mg.

Also available: Butazolidin®, phenylbutazone: Tablets of 100 mg.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
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BU-5412S

for facilitating these contact relationships and correlating information obtained therefrom.

Report—Committee On State Legislation

It was VOTED to refer to a newly-formed Ad Hoc Committee on Problems of Abortion, for study and report, a report of the Committee on State Legislation which proposed that the Society take a position on therapeutic abortion identical with, or similar to, that adopted by the AMA House of Delegates in June of 1967. The Committee recommended that if the Society does adopt such a position, the Committee be instructed as to what steps it should take at the 1969 session of the General Assembly to achieve "liberalization" of the existing Connecticut statutes relative to therapeutic abortion.

Election Of Student Members

It was VOTED to elect to Student Membership twenty-eight Connecticut residents who are enrolled in medical schools throughout the country. The names of the new Student Members will be published in an early issue of the Journal.

Nominations—Medical Advisory Committee To Title XIX Program

Having requested the component county medical associations and all sections and groups that participated in the Relative Value Study to submit suggested nominees for service with this MAC, the President and the Chairman of the Council presented a list of nominees to be offered to Commissioner Shapiro for his consideration and appointment. Having added several more names, the Council VOTED to approve the list, as amended, and to transmit same to the Commissioner.

N.B.: *The foregoing is a summary of the proceedings and actions of the Council on October 18, 1967. Detailed minutes of the meeting are on file at 160 St. Ronan Street, New Haven, for perusal by any interested member of the Society.*

PLACEMENT WANTED

SURGEON—Board certified in General and Thoracic Surgery wishes a group or associate practice in a coastal town. Interested in peripheral vascular, cardiac and thoracic surgery. Has applied for Connecticut license. Military obligations completed.

SURGEON—39 years of age, Board eligible, Connecticut license. Wishes to practice with a group or associate in Connecticut, with no preference to town. Available immediately, no military obligations.

SURGEON—37 years of age, Board eligible, Connecticut license. Wishes to associate with a group or another surgeon. Available January 1, 1968.

OBS-GYN—Board certified, 33 years of age. Presently completing military obligations. Would like to enter into a group or associate practice. Available February 1, 1968.

G.P.—34, currently completing military tour desires to locate in Connecticut. Four years' solo practice experience. Solo, association or group, emergency room, college health. Connecticut license.

CHIEF MEDICAL OFFICER—Challenging opportunity for an experienced physician-executive to head up medical program for a large, progressive, rapid-growth corporation. Location is in midwest, age can vary from late 30's to mid 50's. Income is open and negotiable, benefits are excellent. Company climate is stimulating.

RADIOLOGIST to associate with three Radiologists; expanding hospital and office practice in Hartford area; remuneration: negotiable, leading to full partnership. Contact: Albert C. Hurwit, M.D., 477 Connecticut Boulevard, East Hartford, Connecticut 06108.

PATHOLOGIST—36 years of age, Board certified, Connecticut license. Interested in a group, associate or institutional practice and can be available within one month.

PATHOLOGIST—34 years of age, Board eligible, Connecticut license. Interested in associate pathological practice. Excellent background and training. Available November, 1967.

ANYONE INTERESTED IN THE ABOVE IS ASKED TO CONTACT THE GENERAL MANAGER'S OFFICE, 160 ST. RONAN STREET, NEW HAVEN, CONNECTICUT 06511.

PLACEMENT OPPORTUNITIES

WANTED—young internist, Board eligible or certified to associate with two other young internists in modern, fully equipped building in suburb of Hartford.

PATHOLOGIST—State of Connecticut centrally located general hospital. Must have 2 years' employment in pathology; be eligible for Connecticut license. Salary range: $16,640-$22,180 plus extras. Write: S. Stein, State Personnel Department, 405 State Office Building, Hartford, Connecticut 06115.

ANESTHESIOLOGIST—Board eligible or certified to join small partnership in private practice at the Windham Community Memorial Hospital, 112 Mansfield Avenue, Willimantic, Connecticut 06226.

PEDIATRICIAN urgently needed for community 15 minutes from Hartford with population area of 45,000 people. Opportunity available to head Pediatrics Department in hospital undergoing extensive construction program. Congenial medical staff will help establish. Write: Secretary, Medical Staff, Rockville General Hospital, Rockville, Connecticut 06066.

INDUSTRIAL PHYSICIAN for leading Southern Connecticut manufacturing plant. Modern medical facilities and equipment; staff of five nurses and one assistant M.D. Salary dependent upon experience and qualifications. Excellent fringe benefits, all medical society fees paid. Five-day, 40-hour week.

WELL ESTABLISHED ORTHOPEDIC PRACTICE for sale; excellent equipment; office near major New Haven hospitals; complete files containing case histories and many legal liability matters. Gross $45,000-$50,000 yearly.

WANTED—qualified family doctor to take over practice 30 minutes from Hartford. No obstetrics or orthopedics. Expense-sharing and coverage arrangements with M.D. in same office building. Nearby lab and x-ray. Low price for equipment. No charge for goodwill and introductions. Leaving to specialize. Contact: Lawrence S. Carlton, M.D., 64 Maple Street, Collinsville, Connecticut, Telephone: 693-4017.

G.P.—For limited partnership with another G.P. with eventual takeover of entire practice. Well established practice in a growing town.

OPPORTUNITY exists at present to take over busy General Practice in Southern Connecticut city. General open staff community hospital in area. Excellent professional rapport with local physicians. Transfer of records and equipment by mutual agreement.

Welcome, New Members

New Haven County Medical Association

Victor A. Altshul, M.D., 58 Trumbull St., New Haven, Connecticut 06510

Millard J. Amdur, M.D., Yale-New Haven Hospital, New Haven, Connecticut 06504

Neil M. Barton, M.D., Waterbury Hospital, Waterbury, Connecticut 06708

James C. Branch, M.D., Meriden Hospital, Meriden, Connecticut 06452

Frederick M. Burkle, Jr., M.D., Yale-New Haven Hospital, New Haven, Connecticut 06504

Desmond Callan, M.D., 789 Howard Avenue, New Haven, Connecticut 06504

Denis V. P. Chastanet, M.D., 95 River Street, Milford, Connecticut 06460

Henry T. Clark, Jr., M.D., 272 George Street, New Haven, Connecticut 06511

Michael M. Conroy, M.D., 743 Broad Street, Meriden, Connecticut 06450

Michael T. I. Cronin, M.D., 67 Edgehill Road, New Haven, Connecticut 06511

Ralph J. DePonte, M.D., 123 York Street, New Haven, Connecticut 06511

Adolph Franz, II, M.D., 140 Green Road, Meriden, Connecticut 06452

William L. Gates, Jr., M.D., 144 South Main Street, Wallingford, Connecticut 06492

Alvin D. Greenberg, M.D., 2 Church Street South, New Haven, Connecticut 06519

Irving Guttenberg, M.D., 219 West Main Street, Meriden, Connecticut 06450

Thomas W. Hansen, M.D., Yale-New Haven Hospital, New Haven, Connecticut 06504

Henry E. Helvie, M.D., Waterbury Hospital, Waterbury, Connecticut 06708

J. Michael Hogan, M.D., 47 Cooke Street, Waterbury, Connecticut 06702

Charles R. Jones, M.D., 315 Whitney Avenue, New Haven, Connecticut 06511

Robert Kinstlinger, M.D., 385 Main Street, West Haven, Connecticut 06516

Gustavo S. Montana, M.D., 789 Howard Avenue, New Haven, Connecticut 06504

Hamp S. Pratt, M.D., 377 Broad Street, Meriden, Connecticut 06450

James B. Raybin, M.D., Yale-New Haven Hospital, New Haven, Connecticut 06504

Walter P. Savage, M.D., 2 Church Street South, New Haven, Connecticut 06519

Dominic B. Schioppo, M.D., 1435 Chapel Street, New Haven, Connecticut 06511
A. Herbert Schwartz, M.D., 333 Cedar Street, New Haven, Connecticut 06510
David M. Silverstein, M.D., 5 Maple Avenue, Derby, Connecticut 06418
Martin W. Sklaire, M.D., Wall Street, Madison, Connecticut 06443
Howard B. Spey, M.D., Waterbury Hospital, Waterbury, Connecticut 06708
Theodore L. Strehan, M.D., 1308 Chapel Street, New Haven, Connecticut 06511
Robert M. Vogel, M.D., 380 Boston Post Road, Orange, Connecticut 06477

New London County Medical Association

Clifford J. Hackbarth, M.D., Boston Post Road, Old Lyme, Connecticut 06706
Muzaffer, Kulahcioglu, M.D., P. O. Box 508, Norwich, Connecticut 06360
Dean Lusted, M.D., William W. Backus Hospital, Norwich, Connecticut 06360
Morgan G. Martin, M.D., Box 508, Norwich, Connecticut 06360

Middlesex County Medical Association

Anne C. Wollack, M.D., 1 Essex Street, Deep River, Connecticut 06417

Tolland County Medical Association

George C. Erickson, M.D., Lakeview Heights, R.F.D. #4, Rockville, Connecticut 06066
Robert Lee, M.D., Johnson Memorial Hospital, Stafford Springs, Connecticut 06076

Windham County Medical Association

Carl G. Peterson, Jr., M.D., 150 Mansfield Avenue, Willimantic, Connecticut 06226

Litchfield County Medical Association

James Mason, M.D., 71 Spencer Street, Winsted, Connecticut 06098

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In order to expedite sorting and delivery, the Post Office Department requests that our *Journal mailing carry the zip code.*

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Around The State

184th Semi-Annual Meeting New Haven County Medical Association

The 184th Semi-Annual Meeting of the New Haven County Medical Association was held at Waverly Inn, Cheshire, on Thursday, October 25, 1967. The meeting was called to order at 3:15 p.m. by the president, Dr. Bernard A. Burnham of Waterbury.

The necrology read by the Clerk mentioned the names of eight members departed since the annual meeting in March of this year. The members remained standing after the names were read for a further moment of respectful silence.

We were honored by the presence of Dr. E. Tremaine Bradley, President of the Connecticut State Medical Society and other State Society officers, including Dr. Louis Nahum, Editor of Connecticut Medicine.

The usual full agenda of our meetings was highlighted by the report by the Clerk of the Board of Governors activities, the adoption of the Budget for 1968 and the position taken by the Board on the question of delinquency in attendance at meetings, as provided in the By-Laws.

After election of new members, the Nominating Committee was implemented by elections from the floor of six additional members, one each from each electoral district.

The meeting closed after the adoption of two amendments which had been placed on the table at a previous meeting.

Adjournment was at 5:30 p.m. for social hour and dinner.

Dr. Edward R. Annis, a national figure through his former presidency of the A.M.A. and World Medical Association, his many appearances on t.v. and in the Halls of Congress, the latter to set the lawmakers straight on matters pertaining to Social Security medicine and Medical Care for the Aged, was our honored guest and after dinner speaker.

A large dinner attendance was held in rapt attention while Dr. Annis laid bare the background of his experiences in Washington, the presently awaited changes in Medicare, suggested originally before the passage of the Act, and a look into the future. Before closing, he admonished the profession to become interested in politics, if not through personal efforts, then through co-operation with others whose business is politics.

H. A. Levin, m.d., *Clerk*

MEETINGS

BASIC SCIENCE

Every Other Tuesday 7:15 p.m.
Hematology Lecture Series
Auditorium, Lawrence and Memorial Hospitals, New London
Fee, $100 for 20 Seminars
Description: The Hematology series of courses in Basic Science as Related to Clinical Medicine is coordinated by Robert S. Schwartz, M.D., Associate Professor Medicine, Tufts University School of Medicine, and Chief, Clinical Immunology Service, New England Medical Center Hospitals. Postgraduate credit from the Connecticut Academy of General Practice granted to participants.
Program Director: Edward Gipstein, M.D., Director of Medical Education, Lawrence and Memorial Hospitals. (442-0711 Ext. 361)
Limited to 75 registrants

PSYCHIATRY

January 10 1:30 p.m.
Personality Development and Psychopathology
Kettle Building, Norwich Hospital
Speaker: Maurice E. Linden, M.D., Director of Mental Health, Community Health Service, Philadelphia
Contact: Vincenzo Cocilovo, M.D., Assistant Superintendent, Norwich Hospital (889-7361 Ext. 264)

January 19 1:30 p.m.
Sex Education
Kettle Building, Norwich Hospital
Speaker: William W. Zeller, M.D., Director of Psychiatric Education, Institute of Living
Contact: Dr. Cocilovo
Open to all physicians

SURGERY

January 18 5:00 p.m.
Clinical Advances in Neuroleptanesthesia
Statler Hotel, Hartford
Connecticut Society of Anesthesiologists
Speaker: Guenter Corssen, M.D., Professor Anesthesiology, University of Michigan Medical School, Ann Arbor
Program Chairman: G. W. Valentine, M.D., Waterbury

MEDICINE

January 10 11:00 a.m.
Gold Therapy in Rheumatoid Arthritis
State Veterans Home and Hospital, Rocky Hill
Contact: Richard P. Johnson, M.D., Chief of Medicine (529-2571)
Open to all physicians

January 30 11:00 a.m.
Kidney Transplantation
State Veterans Home and Hospital, Rocky Hill
Contact: Dr. Johnson
Open to all physicians

CONTINUING MEDICAL EDUCATION

Yale University School of Medicine
Anatomy 201: Special Dissection in Anatomy
Course schedule and fee will be arranged
Anatomy 202: Demonstration in Anatomy
Course runs through May 28; fee $175
Epidemiology and Public Health 100: Introduction to Epidiomology
Designed for general practitioners. Course runs from February 20 to March 14. No fee.
Radiology 304: Clinical Laboratory Application of Radioisotopes
Course runs from February 29 to May 16.
Fee $150.

Institute of Living
Course in Psychiatry for Practicing Physicians
First 10-week course underway since November; second 10-week course begins in April. No fee.

NATIONAL MEETINGS

(Consult the Journal of the American Medical Association for details)

January 18-20
National Conference on Community and Emergency Medical Services
Hilton Hotel, San Francisco

January 19-20
American Rheumatism Association
Sheraton-Belvedere, Baltimore

January 20-25
American Academnny of Orthopaedic Surgeons
Palmer House, Chicago

January 29-31
Society of Thoracic Surgeons
Roosevelt Hotel, New Orleans

WOMAN'S AUXILIARY

President
Mrs. Anthony P. Cipriano, Hamden

President-Elect
Mrs. Clarence Harwood, Middletown
First Vice-President
Mrs. Americo Longo, Portland
Second Vice-President
Mrs. Edward P. Allen, Orange

Recording Secretary
Mrs. Nicholas Creaturo, Trumbull
Corresponding Secretary
Mrs. Jacques H. Green, North Haven
Treasurer
Mrs. James Jones, Danielson

HISTORY OF THE LEGISLATION COMMITTEE

In 1922 the Woman's Auxiliary to the American Medical Association was organized. In 1923 the first three committees were appointed: constitution, nomination, and policies. In 1924, legislation was added along with education, finance, and entertainment. In 1926 the legislation committee was changed to Public Relations "and this because the auxiliary wishes to emphasize that it is against the participation of the members in legislative work".

In 1929 the A.M.A. recommended that a Legislative Committee be retained. It might function to influence non-medical legislation concerning women. "You have been asked to inform yourself about bills before Congress affecting the medical profession—this is for education—under no circumstances is the National Auxiliary to participate in any political situations."

But suddenly in 1935, state medicine and compulsory health insurance became the topic on every tongue. The A.M.A. House of Delegates made its second request of the Auxiliary, and we were asked to help alert both our members and the public to the hazards of some of the current medical legislation. (1945).

In 1938, a plan of work was submitted to the Board after repeated suggestions from the A.M.A. president:

1. Have study groups concerned with the present social and economic movements affecting the practice of medicine.
2. Request members to register and vote. "It may be that in the near future every physician's wife will be a registered voter."

From 1935 to 1965 the Auxiliary took an active part in the American Medical Association's efforts to defeat legislation such as the Murray, Wagner, Dingall, Forand, and King-Anderson type bills. With the enactment of P.L. 89-97, Medicare, we returned our focus of attention to other health legislation in which we had formerly spent much time and attention.

Many state auxiliaries have been given credit for materially assisting bringing about the enactment of basic science laws, in defeating laws which would jeopardize the public health by allowing charlatans and quacks to engage in the art of healing, and in preventing the passage of anti-vivisection bills. Auxiliaries have been encouraged to work constructively and effectively for the passage of legislation that is designed to improve the public health.

Since 1957 the auxiliary legislation chairman had been invited to every meeting of the Council on Legislative Activities and participates in the discussion of all bills concerning health which are introduced in Congress.

From the 1938 hope that every physician's wife would be a registered voter, to the present day active participation in politics by Auxiliary members, is a long way. We have come to realize that the election of good legislators will mean good legislation, and we are continuing our fight for the preservation of our freedoms.

Legislation

The overall program of the Committee on Legislation is a continuous process. The more you work in it, the more interested you become, and the more valuable you become. The objectives do not change:

1. To assist the medical profession in the promotion of national and state legislation that will allow the continuation of quality medical care for all people.
2. To inform auxiliary members and the public of the position taken on legislative matters by the medical profession.
3. To assist the American Medical Association and the State Societies whenever requested.

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Keep informed on legislative matters which concern medical practice, health and welfare, and community problems by reading the daily papers and medical publications such as Legislative Roundup and A.M.A. News. Review, comment and inform the auxiliary and the public on health legislation by reports at your meetings, and articles in your publications. Take an active part and participating voice in the affairs and future of the health of our communities.

Take an active stand on legislative measures when requested by the A.M.A. When action is requested, promptness is essential. Consult your medical society and study with them any state legislation needed to improve health care, and interpret the resulting laws to the public.

Become more active and knowledgeable politically. The election of good legislators assures good legislation. Visit Congress and your state legislature during the time that they are in session to become acquainted with the members and procedure.

Consider teaching the techniques of debate and argumentation at your meetings or in special sessions to improve your art of public speaking, not just on the platform, but in daily conversation, so our stand is clearly understood.

Good legislation on all levels is an individual responsibility. The preservation of our liberties and individual rights will remain ours only as long as we continue to work to keep them. Our children will one day inherit the results of our efforts.

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Member Orientation Manual

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BOOKS RECEIVED

Books received for review are acknowledged in this department and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

Synopsis of Gynecology, 7th Edition. Edited by Daniel Winston Beacham, M.D. and Woodard Davis Beacham, M.D. The C. V. Mosby Company, St. Louis, Missouri, 1967. 105 figures and 1 color plate, 384 pp. $8.50.

The Human Adrenal Cortex: its Function throughout Life. Ciba Foundation Study Group No. 27. Edited by G. E. W. Wolstenholme and Ruth Porter. Little, Brown and Company, Boston, 1967. 146 pp. with 26 illustrations.

Antilymphocytic Serum. Ciba Foundation Study Group No. 29. Edited by G. E. W. Wolstenholme, O.B.E.; M.A., F.R.C.P., F.I.Biol. and Maeve O'Connor, B.A. Little, Brown and Company, Boston, 1967. 165 pp. with 37 illustrations.

Myotatic, Kinesthetic and Vestibular Mechanisms. Ciba Foundation Symposium. Edited by A. V. S. de Reuck and Julie Knight. Little, Brown and Company, Boston, 1967. 331 pp. $13.50.

Drug Responses In Man. A Ciba Foundation Volume. Edited by Gordon Wolstenholme and Ruth Porter. Little, Brown and Company, 1967. 257 pp. $13.00.

Doctor's Office

Bennett Barton, M.D. and William N. Hill, Jr., M.D., announce their association for the practice of obstetrics and gynecology at 657 Enfield Street, Thompsonville.

Paul K. Maloney, Jr., M.D., announces his association with R. Glen Wiggans, M.D. and Michael G. Tager, M.D. for the practice of urology at 12 Elmcrest Terrace, Norwalk.

William F. Quigley, M.D., announces the opening of an office for the practice of surgery at 29 Central Avenue, Waterbury.

Ruth Smolen, M.D., announces the opening of an office for the practice of child psychiatry at 1177 Post Road, Fairfield.

Herbert J. Werner, M.D., announces the opening of an office for the practice of pediatrics at 41 Jerome Avenue, Bloomfield.

Edward J. Zyla, M.D., announces the opening of an office for the practice of general surgery at 57 Union Street, Rockville.

OBITUARIES

Martha Louise Clifford, M.D.

1909 - 1967

Dr. Martha Louise Clifford passed away at Hartford Hospital on October 1st from chronic lymphoma.

Born July 21, 1909 in Denver, Colorado, the daughter of William Harvey Clifford and Martha Hoag Clifford, she was educated in the public schools of her birthplace, receiving her A.B. degree from the University of Colorado cum laude in 1930 and graduating from the University of Colorado School of Medicine in 1933. Internship at the State University of Iowa Hospitals in Iowa City began her trek north and east. She attended Johns Hopkins School of Hygiene and Public Health from which she received her M.P.H. degree in 1935 and went from there to her first position as Assistant in the Child Development Study at Harvard School of Public Health.

Joining the staff of the Connecticut State Department of Health as a Public Health Physician in 1936, Dr. Clifford in July of that year was appointed Assistant Director of the Bureau of Maternal and Child Hygiene and in 1937 became its Director, a position which she held until 1951, then becoming Director of the Community Health Division of the State Department of Health.

As a member of the Hartford County and the Connecticut State Medical Society, starting in 1937, Dr. Clifford served various professional committees and groups including the Committee on Perinatal Morbidity and Mortality, Advisory Committee on Nutrition to the Committee on Public Health and the Advisory Committee on School Health to the Committee on Public Health. She held continuing membership in the Hezekiah Beardsley Pediatric Club from the time of her joining the Connecticut State Medical Society and was a charter member of the Connecticut Academy of Preventive Medicine and Public Health as well as being a member of the Connecticut Chapter, American Academy of Pediatrics and the Connecticut Nutrition Council.

In addition to her service to Connecticut medical groups, Dr. Clifford took an active part in such organizations as the American Academy of Pediatrics, American Association of Public Health Physicians, American College of Preventive Medicine and American Public Health Association. In the latter organization she held no less than twenty-two appointive and elective positions including being chairman of the Maternal and Child Health Section and a member of the Governing Council of the organization. Holding an appointment as lecturer in the Department of Public Health and Epidemiology at Yale, she was also active in the Association of State Maternal and Child Health and Crippled Children's Directors including serving as its president and in the Association of Teachers of Preventive Medicine and the National Congress of Parents and Teachers. One of the most gratifying achievements in her life occurred on December 4, 1963 when the Connecticut Public Health Association of which she had been president awarded her the C.E.A. Winslow Award considered to be Connecticut's highest distinction that can come to a public health worker.

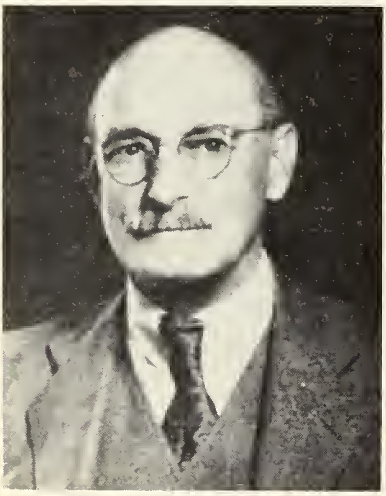
More than twenty-five scientific publications attest to Dr. Clifford's tangible contributions to scientific knowledge and her fellowmen. Accomplishments with which she was directly associated in her professional life included the adoption of the sanitary code regulation for child day care centers, the expansion of dental health clinics, the development of a rheumatic fever and heart disease control program, the establishment of a hearing testing program for preschool children, the licensing of maternity hospitals and the administration of the EMIC program. In April, 1966, more than two hundred of her colleagues gathered to celebrate with her her thirtieth anniversary of work with the Connecticut State Department of Health.

In other areas membership in the American Association of University Women, Zonta International and work with the Connecticut Council of Churches, Business and Professional Women's Club and Young Women's Christian Association earned her friends as well as reflected her lifelong interest in the health and welfare of mothers and children. A cheerful, dignified and sincere person whose simple life and work brought distinction to herself through her dedication to the high ideals of medicine in public health. Dr. Clifford will be missed by her colleagues in Connecticut and public health workers throughout the country.

HAROLD S. BARRETT, M.D.

Roy Lathen Leak, M.D.
1875 - 1967

Dr. Roy Lathen Leak, 92, of West Hartford, retired superintendent of the Connecticut State Hospital in Middletown, died on September 20, 1967 in Bainbridge, N. Y. while enroute home from a short vacation in his boyhood home of Chatham, Ontario.



He was born in Ontario, Canada and came to the United States in 1875 and settled in Watertown, N. Y. He moved to West Hartford in 1944, where he lived until his death. He was a graduate of the Watertown High School and the Albany Medical College, class of 1898.

Dr. Leak began his practice in Watertown in November, 1898, and entered the State Hospital service at Ogdensburg, N. Y. where he practiced surgery until he left in 1911 to join the Matteawan State Hospital in New York.

In 1913 he set up practice in Syracuse, N. Y. and was in charge of the Syracuse Psychiatric Hospital. He was a noted lecturer on medical-legal jurisprudence in the Syracuse Law School. He was also a New York State Medical examiner. In 1917 he went to Columbia, S. C., as medical director of the state hospital. During 1917 and 1918 he served as psychiatrist on the South Carolina State Medical Board. In August, 1918, Dr. Leak was appointed assistant superintendent of the State Hospital at Middletown, Connecticut, now known as the Connecticut Valley Hospital. In July 1921 he became acting superintendent and then superintendent of that hospital from 1922 to 1944, when he retired.

Dr. Leak has been clinical professor of psychiatry at Yale University, now emeritus, consultant at Fairfield State Hospital, consulting psychiatrist at the Veterans Facility in Newington and at Hartford Hospital.

He was a Fellow of the American College of Physicians and a Diplomate of the American Board of Psychiatry and Neurology; past president of the Connecticut State Medical Society; Middlesex County Medical Society; a member of the American Psychiatric Association; founder and past president of the Connecticut Society of Psychiatry. He was also a member of the New England Psychiatric Association; the National Committee for Mental Hygiene; Connecticut State and National Hospital Associations, and the American Medical Association.

Dr. Leak leaves two daughters, Miss B. Louise and Miss Virginia Merle Leak and several nieces and nephews.

Dr. Leak had a long and distinguished record in psychiatry. He was a firm believer in the early and preventative treatment of the mentally disturbed; he advocated separate hospitals for the treatment of the aged. Not only was he a distinguished psychiatrist and a superior administrator, he was also a loyal and true friend. To adequately handle the variety of responsibilities which he assumed and enjoyed required an unusual combination of talents and one of these was devoted to making and keeping friends.

Finally, one of the traits I remember best was his consistent modesty; he never pursued the spotlight. He was a quiet but persuasive source of inspiration to those he supervised and to many others.

DANIEL P. GRIFFIN, M.D.

In Memoriam

Findorak, Francis G. — Bridgeport, Georgetown University School of Medicine, 1932. Dr. Findorak had been engaged in dermatology and syphilology in Bridgeport for over 15 years. During World War II, he was a Captain in the Medical Corps. Dr. Findorak was associated with the Bridgeport and St. Vincent's Hospitals. He was a member of the Fairfield County Medical Association, the Connecticut State Medical Society, and the New England Dermatology Society. Dr. Findorak died November 6, at the age of 61.

Hymovich, Leo — Stamford, Jefferson Medical School, 1929. Dr. Hymovich was a practicing surgeon in the Stamford area for over 30 years. During World War II, he served in the Medical Corps in the United States Army. Dr. Hymovich was past president of the Stamford Medical Society and member emeritus of the staffs of Stamford and St. Joseph's Hospital. He was director of the medical board of the Rehabilitation Center and director of the Industrial Medical Association. He was a member of the Stamford Medical Society, the Fairfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Hymovich died October 22 at the age of 63.

Mastrony, Paul C.—Bridgeport; Catholic University of Louvain Medical School, 1959. Dr. Mastrony was a physiatrist and director of the Department of Physical Medicine at St. Joseph's Hospital, Stamford. He was a U.S. Army Veteran of World War II. He was a member of the Stamford Medical Society, the Fairfield County Medical Association, the Connecticut State Medical Society, and the American Medical Association. Dr. Mastrony died August 26, at the age of 40.

Starrett, Jay E.—Stamford; Tufts Medical College, 1930. Dr. Starrett was a urology specialist in Stamford for the past 35 years and was associated with the Stamford and St. Joseph's Hospitals. From 1942 to 1946 Dr. Starrett was a lieutenant colonel in the Air Force. He was a past director of the Stamford Hospital's Department of Urology, and past president of the Stamford Medical Society and the Stamford Hospital medical staff. He was a member of the Stamford Medical Society, the Fairfield County Medical Association, the Connecticut State Medical Society, the American Medical Association, and the Connecticut State Urological Association. Dr. Starrett died October 16, at the age of 63.

News From Yale University School Of Medicine

Announcement of a new organization, the Medical Center Housing and Community Development Corporation, was made recently in a joint statement by Charles H. Costello, President of the Yale-New Haven Hospital, and Dr. F. C. Redlich, Dean of the Yale School of Medicine.

Edward S. Gruson of Boston, an urban planner, has been named President of the new corporation. Mr. Gruson's experience includes planning for health services and facilities in Boston and Mound Bayou, Mississippi, as well as for housing in Puerto Rico.

The objectives of the corporation are to plan for and develop housing and community facilities related both to the needs of the Medical Center and to the interests of the community as a whole. To achieve these objectives, the corporation will strive to integrate its activities with those generated in the Hill neighborhood as well as with the work being undertaken in that area by public and private agencies.

The decision to establish the new corporation reflects the Medical Center's commitment to cooperate in the renewal of the neighborhood in which it is located, according to Mr. Costello and Dean Redlich. "Planning for the future development of the Medical Center must be carefully coordinated with many other developments occurring in the Hill area," the joint statement said. "The new corporation will provide the means for the Medical Center to work closely with the City and with neighborhood groups in planning for the anticipated model neighborhood program in the Hill."

* * * *

Yale University recently announced preliminary plans for a new $7 million research tower for surgery, obstetrics and gynecology at the Yale-New Haven Medical Center.

Tentative plan call for a start on construction of the Laboratory of Surgery, Obstetrics and Gynecology in the latter half of next year and for completion of the building in about two years. Private and public financing is expected to provide the necessary funds, according to Dr. F. C. Redlich, Dean of the Yale School of Medicine.

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NEW BOOKS IN REVIEW

NEW DRUGS. 1967 Edition. Evaluated by A.M.A. Council On Drugs. American Medical Association, Chicago, 1967. 590 pp.

Reviewed by: LOUIS H. NAHUM

New Drugs contains fifty one chapters with an appendix, index and calculation of drug dosage for children. The chapters are organized primarily on the basis of major therapeutic use of the new drugs described. Each of these therapeutically oriented chapters describes briefly the relationship of newer to older drugs and incorporates the essential information the practitioner needs. The information includes the generic, chemical and trade names, actions and uses, indications, and contraindications, adverse reactions, dosage, preparations and suppliers.

Because the book covers virtually all single entity prescription drugs which have been introduced over the past ten years, it becomes a concise therapeutically organized compendium of the major useful single entity drugs to which the physician has access where possible valid comparisons are made between the available therapeutic agents. The available therapeutic uses of drugs discussed is indexed, and the drugs themselves are indexed by both their non-proprietory and trade names.

The book is extremely useful to the practicing physician because it is an authoritative product of many celebrated consultants. Unresolved areas though minimal are resolved by a referee selected from the Council on Drugs membership. Thus the monograph is a distillation of practically all published and unpublished data.

In the area of drug evaluation we know of no other parallel effort which has at its disposal both manufacturer's and research resources and uses them so fully in order to insure authoritativeness and completeness of the drug information provided in New Drugs. It is being published and distributed by the A.M.A. to lower cost and promote wide distribution to the medical profession. It is an entirely new book invaluable to the practicing physician. The unanticipated extent of the "drug explosion" has made this book a must for each member of the medical profession and much paramedical personnel.

INFANT NUTRITION. Edited by Samuel J. Fomon, M.D. W. B. Saunders Company, Philadelphia and London, 1967. 299 pp. Illustrated. $10.50.

Reviewed by: JOYCE GRYBOSKI

This monograph, well written and well documented, is to be recommended to the physician interested in growth and nutrition, and their associated problems. It is in large part a reference text rather than one to be read and digested within several evenings. An early chapter, "Normal growth and failure to thrive" stresses the interesting concept of incremental growth, i.e. the average daily gain over a period of time as being more sensitive than the standard growth charts in which a particular infant may be expected to progress along a specified growth channel.

The digestion and absorption of carbohydrates, fats and proteins are discussed rather briefly and superficially, although considerable attention is given to their nutritional requirements. Sugar absorption is discussed in most detail with some reference to the disaccharidase deficiencies and lactose or sucrose intolerances. Monosaccharide malabsorption, a more recent entity is not included. Excellent tables are provided which include the protein, fat and sugar compositions of the usually available infant formulas and foods.

Vitamin and mineral requirements are presented and most are discussed briefly superficially, with attention to any clinical manifestations of deficiencies only for the major vitamins and minerals. Iron deficiency anemia, and calcium: phosphorous ratios of the various formulas are presented in detail. Tables of potential renal solute load from ingested formulas or infant food are invaluable for those dealing with any patient who has impaired renal function.

In later chapters, the antigenicity of milk proteins in the various formulas is discussed and complete components of nearly all of the commercial formulas are provided. An excellent chapter lists the soy substituted formular and the non-soy milk free formulas, valuable for the treatment of milk protein allergy, lactose intolerance and some of the metabolic disorders. A table is presented listing the hereditary metabolic diseases and their known therapeutic management. Several references are listed for each disorder.

In general, the book is to be highly recommended as a reference text. At times is seems overweighted with tables, but many of these same tables compile data in an easily accessible form which may save hours of research for the reader. This reviewer would have enjoyed in addition, some discussion of infant malnutrition, its associated metabolic disorders and its therapy.

RESPIRATORY PHYSIOLOGY. Edited by N. Balfour Slonim, M.D., Ph.D. and John L. Chapin, Ph.D. The C. V. Mosby Company, St. Louis, 1967. 199 pp. $8.75.

Reviewed by: LOUIS H. NAHUM

The material in this book is derived from experience gained both in teaching physiology and practicing medicine and is aimed at the medical student but will prove of value to the physiologist, environmental scientist, physician and even certain paramedical personnel.

There is present material on the respiratory aspects of pH., homeostasis, responses to unusual environments and special atmospheres and clinical evaluation of pulmonary function. There are some illustrations of electron micrographs of healthy human lungs. The mathematics is not too difficult for the student to understand and since it is the language of science and therefore of physiology, it lends itself to the kind of objective and precise expression which is necessary to clarify fundamental concepts in respiration.

There are twelve chapters, an appendix with values needed in physics and chemistry of respiration, some questions and problems, an excellent glossary of terms and selective references at the end of the book. The book is beautifully printed, the illustrations are clear and pleasing to view. Only one misplaced decimal point was found in the whole book and this was the atomic weight of zinc which should read 66.5.

The book is recommended as an excellent volume for students in physiology, for cardio respiratory fellows and the studious physician.

MEDICAL NEWS

Transfusion of Blood Components

Transfusion of whole blood is generally needed only in hemorrhage severe enough to cause shock and anoxemia. More often, the patient needs certain blood components, not whole blood, and it is generally more economical and safer to administer those specific components. This special issue of The Medical Letter describes the various components and lists the indications for which each is preferred or for which it provides an alternative therapy.

In many centers blood is collected by closed-system methods using sterile plastic tubing and bags, and is then separated by differential centrifugation into such components as red blood cells, platelets, antihemophilic factor (AHF) and plasma. Plasma itself can be used to supply stable clotting factors, or it can be further fractionated to yield fibrinogen, albumin, and gamma globulin. As examples of the use of components, a patient with severe anemia due to hemorrhage can be given red cells; one with thrombocytopenia, platelets; one with classical hemophilia, AHF-rich cryoprecipitate; and one with deficiency of a stable clotting factor, stored plasma.

PACKED RED CELLS — Packed red blood cells can be used in any severe anemia due to hemorrhage which does not require restoration of blood volume. It has been estimated that 80 to 90 per cent of transfusions can be given as packed red cells (J. M. Vogel and P. Vogel, Anesthesiology, 27:363, 1966). The use of packed red cells instead of whole blood reduces the danger of circulatory overload by decreasing the amount of plasma colloid and sodium infused; it also reduces the quantity of potentially harmful isoagglutinins and minimizes reactions resulting from the presence of food or drug allergens in the blood, as well as reactions which may be caused by leukocytes and platelets.

LEUKOCYTE- and PLATELET-POOR RED CELLS – The incidence of reactions which may be due to leukocytes and platelets can be reduced by removing from the blood or packed red cells the buffy coat and the supernatant plasma, either by centrifugation or by gravity (with the bag or bottle in an inverted position, blood is allowed to settle and the red cells are drawn off from the bottom). To assure sufficiently complete removal of leukocytes, platelets and residual plasma, the red cells must be washed two or three times with a sterile isotonic solution. This procedure is laborious and predisposes to bacterial contamination; it should be used only for patients with severe hypersensitivity to leukocytes or platelets.

FROZEN RED BLOOD CELLS – A new and as yet experimental method for freezing red blood cells is reported to preserve them for one year or more (A. W. Rowe et al., Transfusion, 6:521, 1966). If early experience is confirmed, it will be possible to store rare blood types in a frozen state. (A list of persons having these types of cells is kept by the American Association of Blood Banks, 30 North Michigan Ave., Chicago, Ill.) It will also be possible to preserve a patient's red cells for his own use, thereby eliminating the risk of infusing the hepatitis virus or antigens to which the patient was previously sensitized. The preparation of frozen red blood cells is, however, laborious and requires the addition of an agent such as glycerol to assure a uniform rate of intracellular crystal formation. After thawing, the cells must be washed several times to remove the glycerol.

PLATELET TRANSFUSIONS – A unit of platelet-rich plasma (PRP) contains 80 to 90 per cent of the platelets normally present in a unit of fresh whole blood; most indications for platelet transfusion require several units of PRP. Platelet concentrates are prepared from PRP by more prolonged centrifugation; they are about as effective as PRP and have the advantage of eliminating the risk of circulatory overloading. Platelets are usually administered for thrombocytopenic hemorrhage; in some centers they are given to patients with severe thrombocytopenia even when there is no bleeding, to reduce the frequency of cerebral hemorrhage.

GRANULOCYTE TRANSFUSIONS – Granulocyte transfusions have had widest use in the management of white blood cell depression following therapy with anti-tumor drugs. The number of granulocytes believed to be needed to improve response to infection can best be obtained by plasmapheresis from patients with chronic myelogenous leukemia who have had a high proportion of polymorphonuclear forms, with peripheral counts of 100,000 cells per cu mm. Even when the granulocytes are available, however, their efficacy is debatable (E. J. Freireich et al., Ann. N. Y. Acad. Sci., 113:1081, 1964).

PLASMA — The use of plasma has decreased in recent years because of the availability and superiority of whole blood or packed red blood cells for the treatment of hemorrhage, and because the use of plasma from pooled blood is associated with a high incidence of hepatitis. Storage of plasma at 31.6°C for six months has been used to reduce the risk of hepatitis infection, but recent experience raises questions about the efficacy of such storage.

The chief indication for plasma is in the treatment of coagulation deficiencies; plasma can supply clotting factors quickly and in great quantity without raising the hematocrit above normal. Freezing of the plasma is necessary to preserve the labile clotting factors, V and VIII (AHF). All other clotting factors (VII, IX, X and XI) are present in non-frozen preparations. Frozen plasma can be prepared from freshly donated blood after removal of all cellular elements. Frozen dried plasma when reconstituted contains an amount of antihemophilic globulin comparable to that contained in the frozen liquid plasma.

Both frozen and non-frozen plasma can be prepared from single-donor or pooled blood. In pooled plasma the isoagglutinins are neutralized, and it can be handled in bulk and distributed as a pharmaceutical product. Because of the increased risk of hepatitis, however, plasma from a single donor is preferred.

Suggestions for LSD Treatment

Suggestions on treating the rising number of victims of LSD and other hallucinogenic drugs are offered the nation's physicians in the current Journal of the American Medical Association.

Comprehensive treatment, however, goes far beyond routine, first-step measures, warns a statement by the AMA's Council on Mental Health and Committee on Alcoholism and Drug Dependence.

The problems of drug dependence are so complex that the physician may find he needs all the help he can get. He may need to call on the services of psychiatrists, other medical specialists, and the community's other professional resources, such as clergymen, educators, social service agencies, and attorneys.

"Hallucinogen-induced dependence is psychological," the statement said. "The drugs have a particular attraction for adolescents and young adults who are socially maladjusted or emotionally inhibited and who constantly seek new 'experiences' and 'insights' ".

Drug dependence "is almost universally symptomatic of underlying personality problems, severe neurotic conflicts, or psychotic reactions," according to the AMA statement.

Thus, an important step in the physician's treatment is to determine "what is really bothering (the drug user) at both conscious and unconscious levels." The physician also has to learn how these needs are met by drugs. Only then can the doctor, with the help of other professionals, offer complete treatment.

It becomes the physician's task to help the patient comprehend his phychic and personal problems, and how to cope with them.

"Short of this, the physician may have to give long-term supportive therapy that will enable the patient to live a productive and satisfying a life as possible with his psychic handicap and in a drug-free state."

At least three types of users of hallucinogenic drugs have been noted:

One consists of narcotic drug-dependent persons who take LSD or other hallucinogens infrequently after a "fix" with narcotics.

Another group includes users of other drugs, especially marihuana, who relish the more intense effects of hallucinogens.

A third group is composed of persons who repeatedly take LSD only or in combination with other hallucinogens over a sustained period of two weeks to a month. Unlike those in the second group, they take the drugs not for social purposes, but to achieve "some personal, esoteric goal."

A variety of complications have been reported, but three appear to be most prevalent.

1. Reappearance of the hallucinated, disorganized state without drug-taking. This has occurred within two months after a series of relatively few exposures to hallucinogenic drugs. It also occurred more than 12 months after one person took the drugs more than 200 times over a period of years.

2. Panic is a frequent complication. "Hospitalization may be sought by the user or his companion, neither of whom can cope with the sense of terror."

3. A third, relatively common, complication is an extended period of psychosis, sometimes after a single exposure to drugs, and usually involving a person who was "prepsychotic" or had a history of psychosis.

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